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THE PROBLEM OF SOCIAL MEDICINE: EQUILIBRATING THE DISTRIBUTION AND TECHNOLOGY OF MEDICAL CARE*

WINSLOW CARLTON†

NEW YORK CITY

NO SUBJECT calls more insistently than social medicine for a disclaimer of omniscience. Medicine as a social institution is peculiarly complex both in structure and in function. This paper essays only to indicate the nature of a central problem and to suggest a few principles for guidance toward solution.

Throughout the United States today, one element in the distribution of medical care is under sharp attack. Strong political forces are pressing for a new way of paying for medical services. On the principle that all people have an equal right to the benefits of medicine, it is proposed that the Government cover the costs. Although many opponents believe that the movement "to socialize" medicine, as the attempt has been labeled, reflects no more than the desires of a small but vocal radical group, there is substantial evidence that the prevailing system for distributing medical care is not, in fact, appropriate to the technology of medicine.

To put it bluntly, the present system does not succeed in delivering to most people anything like the scope and quality of services of which modern medicine is capable. Formal sociologic studies conducted over the past thirty years provide statistical evidence in support of that conclusion, and observation of medical conditions in a variety of communities confirms it. There is no need to enumerate the quantitative findings: the principal ones have been conveniently assembled in a publication of the Social Security Board entitled "Medical Care and Costs in Relation to Family Income." What should be said is that these statistics require interpretation in the light of clinical observations. Without a knowledge of how medicine, as a social organism, actually functions, it is easy to conclude that a great deal of money collected and disbursed by the community at large will effect a cure.

Observation of conditions in New York City leads, I believe, to substantial modification of that conclusion. There, it is true, are most of the medical prerequisites: although it could do with more of almost everything, New York is rich in medical resources compared with many other communities. It must be added that the impressions recorded below have been distilled from the experience of eight years' effort to establish a voluntary system of prepayment for medical care in New York City.

The undertaking offers considerable advantages for purposes of observation, since such prepayment plans deal with both the suppliers and the recipients of medical and allied services. Enterprisers in this field — they might be called "adventurers" if one had a mind to, and many doctors have — are necessarily observers of how medicine actually works. One sees physicians in practice and learns what they expect of medicine and what they realize; concurrently, the patients disclose what they expect of medicine, how they go about getting it and what they get.

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Our first conclusion is that nearly half the cases of illness occurring among New Yorkers of average income do not reach a physician or any other person of medical experience. With our wealth of resources, — including physicians, hospitals, clinics and social services, — virtually all emergency cases receive medical attention. No such statement, however, can be made about other illnesses. The evidence for this conclusion comes from experience with a prepayment plan operated by Group Health Insurance from 1938 to 1944 that was almost identical in scope of services with that of Boston's recent White Cross plan. It covered virtually all types of physician's care. Any licensed physician was eligible to participate, and a panel of three hundred and fifty general practitioners and a hundred and fifty specialists was developed. The maximum number of subscribers enrolled at any one time never exceeded fifteen hundred. The plan, obviously enough, was not a practical success, but something was learned about the existence of un-

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†Chairman, Board of Group Health Insurance, Incorporated, New York.

treated conditions and what happens when the barrier of fees is removed.

One feature of the plan was a preadmission medical examination conducted by general practitioners selected from the panel by the applicant, and it should be noted that the Medical Board found a great variation in the quality of the examinations. According to the reports submitted, conditions requiring medical attention were found in 30 per cent of the applicants, and the nature of the conditions suggested that fully a third of these had not received such attention. When it is considered that the majority of the subscribers were acutely conscious of their health or at least more aware of medical care than the average person, as indicated by the fact that they had joined the plan, it is evident that a substantially higher proportion of the population at large are avoiding medical attention.

After admission to the plan, the subscribers averaged about six yearly calls on a general practitioner — that is, the participating physicians had six hundred calls per hundred subscribers, of which five hundred and fifty were in the office and fifty at home. It has been reliably estimated that this over-all figure represents about double the number of services used under postpayment. The participating physicians who had the largest practices reported only a negligible amount of hypochondria or abuse of privilege among the subscribers; the overwhelming majority of calls were for illness, organic or functional, that needed medical attention. Although many of the conditions were not important, others were, and the uninformed patient had no way of distinguishing one from the other except through pain.

The second, and more surprising, fact disclosed is that interest in and concern for the maintenance of the patient's health is the exception, not the rule, among general practitioners. The reason is not far to seek: there is little effective demand for personal preventive medicine. Whatever the practitioner may have learned at medical school and the hospital, the services for which patients seek care and pay determine the direction of his interest. The treatment of acute upper respiratory infections, gastrointestinal disorders and children's diseases, the reduction of fractures and dislocations and attendance on obstetric cases comprise the average general physician's practice. Thorough physical examinations and, except for hypochondriac patients, consultation on general conditions of health are not sought.

Also impressive was the contrast between the coordination of care effected by practitioners affiliated with leading hospitals when their patients needed specialist attention and the lack of co-ordination in similar cases when handled by practitioners without good hospital connections. Numerically, almost a quarter of the subscribers were judged by the general physicians to require some type of specialist service in the course of a year. It is believed that closer association between practitioners and specialists, such as that created by group practice, would raise this proportion, high though it already seems in comparison with the 15 per cent often cited.

Finally, the most striking phenomenon observed is the degree of ignorance shown by people in all walks of life concerning both what medicine has to offer and how to go about obtaining medical attention. Only about a third of the people in New York have a family physician, according to a survey made several years ago. Whereas this proportion is doubtless lower than would be found elsewhere, there is little doubt that the institution of the family doctor has declined sharply the country over during the past quarter century, and nothing has taken its place. The result is that an ever-increasing number of people are medically adrift. In the classic sense of the term, they might be called the "medical proletariat." To these people, physicians are to be called, like the fire department, in emergencies only. And when the emergency arises, they find that they do not know whom to call. There is evidence of a growing reliance on hospitals as sources of medical referral, but the testimony of a relative or friend, the corner druggist or merely the shingle by the door is usually decisive.

Still another sign of dislocation is the drift of these unattached patients to specialists, or to those whom they believe to be specialists. Everyone who is not a physician has great faith in his ability to diagnose his own ailments, and the patient with a backache is taken to "Mrs. Smith's wonderful bone specialist." An internist of my acquaintance wryly remarked that in a surprising number of these self-referred cases, the patient's diagnosis is confirmed.

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This review of deficiencies in the distribution of medical care, fragmentary and impressionistic though it is, may seem an effort to frame an indictment. It is not; the purpose is rather to delineate a problem. American medicine as a social institution is out of balance: the medical arts and sciences are capable of far more than the distributive system delivers. And in one broad and important field — namely, the conservation of personal health — the limitations of distribution are reducing technology to a state of virtual atrophy.

The question now facing us is how, precisely, to reform the system of distribution to provide better, as well as more, medical care. Certainly, the answer is not a simple one. Anyone who has been closely associated with medical care must realize that much that is actually and potentially best in medicine is volatile. For all that the physical sciences have contributed to diagnosis and treatment, a large part of the physician's technic is the product of art rather than of laboratory science. The physician retains many of the attributes of the priesthood

from which his profession sprang. He cannot be merely the technician, processing each patient who appears before him on the production line.

A further point of criticism is that a considerable amount of medical care rendered under present conditions is mechanical. Patients reporting to the outpatient departments of some teaching hospitals are not uniformly treated with consideration and respect, although given all possible laboratory tests and x-ray examinations. In the New York plan, we found more physicians possessed of technical competence than those also equipped to deal with their patients as people. It seems likely that this has a bearing on the failure of the public to seek preventive services and to maintain consistent medical relations.

Anything done in the future should certainly be designed to avoid sterile mechanization. Rather, the conditions under which medical service is rendered should provide incentive for the development of the personal relation between physician and patient. If this could be accomplished, there is no doubt that more emphasis would be placed on the education — in contradistinction to the training — of those entering medicine and that psychology and psychiatry would receive more attention both in the curriculum and in research than they are now accorded.

The second requirement placed on reform must be in the interest of the physical sciences. This is given second place because scientific development is in large part a function of broader forces than medicine controls. It ebbs and flows with basic social and economic conditions, and so long as America remains economically strong and socially dynamic, great energy and large resources will be channeled into basic scientific research. But the system of medical distribution should contribute to the multitude of undertakings required either to adapt the products of pure research to medical use or to investigate the nature and causes of disease. At present, only from the distribution of drugs and medicines is there a financial contribution to research that stems directly from the users. Otherwise, the distributive system does not automatically produce the sinews of development. For the rest, medical research is dependent on the charity of individual physicians donating time, of philanthropists providing endowments and of foundations making grants. A small amount, which may soon be larger if current efforts in Washington succeed, comes from government. Clearly, it is not inherent in the nature of medicine to depend on benefactions for so vital a part of its work. It is merely that society has not yet caught up with the change that has taken place since the principal source of medical care was the church. No one suggests that voluntary contributions to the cause of medicine should not be welcomed; it is only that the degree of dependence on charity is no longer appropriate to the task.

It should be added that since the public is now orientated toward medicine, an additional charge labeled "for scientific research" on bills for professional or hospital services would probably meet with less resistance than an equal charge for personal preventive services.

The financing of hospitals has more nearly kept pace with their evolution than has that of research. Here, a change of functions since the days when hospitals were pesthouses and hostels is obvious. As prime requisites in both the production and the distribution of medical care, the distributive system should effect adequate means of support. To make up present deficiencies in certain parts of the country, the expedient of federal aid as embodied in the Hill–Burton Act, recently adopted by Congress, seems desirable, but it would surely be functionally and organically sounder to place hospital financing directly into the total medical scheme. We are well on the way to doing that; the deficits of our voluntary hospitals in New York are down to less than 10 per cent of operating costs.

Obviously, a reformed system of distribution should contribute more than money to the development of medical research. It should be so constructed that physicians and others with a bent for investigation are given an opportunity to participate in systematic research without having to establish themselves in a metropolitan center. Smaller communities need that caliber of professional ability and interest. The mechanical difficulties involved are obvious and great, but the concept of central hospitals with satellite institutions and staffs is already current and attempts to apply it have been started.

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The final criteria of an adequate distributive system for medicine are both economic: in the first place, the personnel and facilities should be organized for maximal efficiency; and secondly, the cost of producing and distributing medical care should be equitably apportioned.

The word "efficiency" carries a connotation of regimentation and mechanization that it ill deserves. That is efficient which most directly accomplishes the purpose. The purpose under consideration is to provide a complex personal service, whose main elements I have attempted to define. Thus, it would not be efficient medicine for this hospital to employ ten doctors from nine to five for five days a week to give physical examinations and only physical examinations. By the same token, it is not efficient medicine — no matter how great the apparent saving in dollars — to rotate clinic staffs in such a way that each time a patient visits the clinic he is seen by a different physician.

But to the extent that professional time and expense and the time of the patient can be saved without sacrificing necessary thoroughness and the personal relation, efficiency is gained. Medical group practice seems able to attain that end. Coordination of the patient's care is facilitated by staff organization, specialized facilities and unit case records. Hours of patient time and at least quarter-hours of doctor time are saved when special procedures or consultations are required. If these savings applied to only 15 per cent of cases, they would be important, but as noted above, the experience in New York suggests that a substantially higher proportion need the attention of a specialist. In addition, group practice reduces the expenses of the individual physician, practitioner and specialist alike, because facilities and ancillary personnel are shared. With everything taken into account, it is not an exaggeration to say that group practice can increase the efficiency of delivering medical services by 50 per cent.

Of course, no institution is better than the people who serve it, and medical-practice groups follow the rule. They do not guarantee a high standard of medicine; all they offer is a device to make good medicine easier to produce and cheaper to deliver. As such, they are key points in the reform of medical distribution.

The final requirement placed on reform is that it shall equitably apportion costs over the population. Health insurance is one method — voluntary or compulsory, or both. Direct taxation to raise the needed funds in whole or in part is still another method. But before any money is raised or insurance premiums are paid, the public should know precisely what is to be paid for and how the quoted cost was arrived at.

For example, a system of insurance that applied the methods and fees of the New York Workmen's Compensation Act to medical care for the population as a whole would raise the national health bill from four or four and a half billion to something over ten billion dollars. If, on the other hand, group practice were prevalent so that fixed-rate payments could be made to medical groups, the same quantity of service would cost only about seven billion dollars. (I say "only" advisedly: the amount would still be less than that spent on automobiles.)

It must immediately be said that these estimates cannot pretend to be precise, for experience with prepayment in this country is limited. At most, 10 per cent of medical costs are now paid through insurance, and the great bulk of that goes for hospitalization. Regarding professional services, experience is fragmentary and diverse — indicative but in no way conclusive.

In view of the paucity of experience, particularly the widespread ignorance of what medicine can and should be, the proposal to set up an all-inclusive, federal system of paying for medical care seems premature. Although we may know enough to take the first strokes, it does not seem judicious to leap off the dock.

Nevertheless, it must be recognized that a large number of people in the United States cannot afford to pay, by themselves, for even the most efficiently delivered medical care. Whole areas now suffering from medical impoverishment cannot possibly support an adequate standard out of their own resources. It is unreasonable to suppose that these deficiencies can be made up without bringing the tax power into play. Medical care is surely an appropriate object of community expense, not only as a means of relieving suffering but also, even more, as a measure for raising the general capacities of the people. If properly expended, public monies disbursed for health services constitute an investment.

The art is to spend the funds properly. That we must learn, as we learn any art, by doing and closely observing the results. "*Far una prova*," the Italians call it — "to make a proof," rather than to wait for proof to arrive. Active experimentation at the local level is what is needed most.

It is pleasant to be able to report that New York is at work. The most notable attempt in this country to put into practice, on a community-wide scale, the concepts of medicine implied in this paper is the Health Insurance Plan of Greater New York, which, after more than two years of arduous preparation, should be in operation by the new year. But many similar attempts are needed throughout the Nation, and they should not be delayed. Only local knowledge gained by experience, as well as local understanding of what medicine is and can be, will ensure the delivery of good medicine in the future.

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The restoration of medicine as a social institution to a state of equilibrium within itself is a job crying for the participation of the most highly qualified physicians. Thus far, leaders in the profession of medicine have taken an active part in only a few communities; leaders in the business of medicine have taken rather too great a part. Why is this not a subject for the medical schools? It is as much a matter of concern to medicine as foreign policy is to government. Statesmanship is needed, and where else should one look than to the medical schools?

What is required is the creation of a new discipline within medicine — it might properly be called "social medicine," which would concern itself with the relation of the medical arts and sciences to society. It is not a subject to be handled as an extracurricular activity at occasional institutes and conferences; it demands the same kind of concentrated attention and expertise as any major field of investigation and practice. Training in medical administration will not answer, useful though administrators would be, for something worth administering is necessary. Nothing less than organized

staffs of men and women working in the community, observing medical conditions with painstaking care, consulting the experience of representative people, examining the results of local medical plans and interpreting their findings as scientists will produce sound answers to the fundamental questions at issue.

The problem of social medicine is now acute, but so long as American society remains dynamic, the problem will also be chronic. Changes in general society and within medicine itself will call for constant adjustment of the distribution and technology of medical care to maintain a balance. Only consistent, scientific examination of the people's health and evaluation of the findings in the light of broad social understanding will achieve the flowering of medicine that now lies in the wood.

THE TEACHING HOSPITAL'S SERVICE TO THE PUBLIC*

ALLAN M. BUTLER, M.D.†

BOSTON

THAT ether was introduced into the practice of medicine in a hospital such as the Massachusetts General Hospital was not an odd chance. Such a large teaching general hospital provides the various factors essential to the intelligent introduction of new therapeutic agents and technics to medical practice. Indeed, the actual application of all new medical knowledge must almost always be accomplished through such a hospital. Where else can be found an adequate number of patients under the close and continuous observation of competent physicians who have the appropriate training, the curiosity, the time and the support of adequate laboratory facilities and personnel? The fact that such therapeutic agents as x-rays, radium, the sulfonamides, penicillin, streptomycin and the radioactive isotopes were introduced into medicine through teaching hospitals demonstrates their particular suitability for determining the methods by which the contributions of science may be applied to the care of patients. Moreover, the clinical investigator is often the first to see the clinical application of scientific knowledge. Although his role usually falls under the category of applied science, his contact with both clinical medicine and scientific thought and technic gives him interests and opportunities that the basic scientist may not have. The experimental contributions of the clinical investigator, therefore, may open fields that basic science and industry may cultivate with great profit.

The discovery of the anesthetic value of ether by Long, a physician, and Morton, a dentist, that is commemorated today opened a field of scientific investigation to chemists and physiologists that was effectively cultivated by industry to the great benefit of society. Banting, an orthopedic surgeon, and Best, a medical student, discovered insulin. Clinical investigators in hospitals such as this perfected the application of this new therapeutic agent to clinical medicine; chemists produced the crystalline substance and developed other compounds; industry made them available by mass production; and millions of patients with diabetes and other equally serious ailments benefited. Drs. Minot and Murphy, both clinicians in the teaching hospitals of Boston, by discovering the effectiveness of liver in the treatment of pernicious anemia similarly contributed not only a specific therapy for a human ailment that had previously been fatal but also ideas that stimulated scientific work and provided opportunities for pharmaceutical endeavor that have been pursued efficiently. Fleming, working on the bacteriocidal property of tears, and Waksman, a soil bacteriologist, discovered, respectively, penicillin and streptomycin — therapeutic agents that have revolutionized medicine by reducing morbidity and mortality and that have resulted in expanding industrial activity and earnings. What does it matter whether these contributions are basic, biologic or applied science? For science is no end in itself. Their significance is that they are contributing to human health, wealth and happiness. Can the same be said of atomic energy, the latest contribution of basic science?

An extreme and puzzling example of the unique position of the clinical investigator and the teaching hospital arises in a consideration of how investigation of the prevention and treatment of mental disease will be advanced. Are we to rely on the basic sciences to break through the impasses that now confront us in this most distressing and costly field of medicine? Or should we support the clinical investigator, whose approach to the subject appears so unscientific to the scientist? I shall not attempt an answer, but shall venture the guess that the contributions that will ultimately open this field to scientific exploration will come from clinical investigators working with patients in teaching hospitals, not from basic scientists working in laboratories with mice or test tubes, or from the psychiatrists of overcrowded and underfinanced mental hospitals. The opportunities offered by the patients,

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†Professor of pediatrics, Harvard Medical School; chief, Children's Medical Service, Massachusetts General Hospital.

staff and research facilities of this hospital, with its department of psychiatry in intimate association with every division of this general hospital and with the McLean Hospital, were thoughtfully conceived and are being well pursued. But the personnel of both that department and the McLean Hospital are inadequate — inadequate in terms of diversity of training, number and especially time free of the overwhelming demand for the meager therapy that is available today.

A teaching hospital not only provides the facilities essential to clinical investigation but also develops groups of investigators that are larger and more enduring in life, though not in memory, than the individual. These groups, led by the Churchills, Meanses, Cobbs, Aubs, Bauers, Albrights, Whites and others, are continually working for all of us and our children not only by their contributions to new and better medicine but also by educating your and all physicians and by caring for patients. They largely provide the stock in trade of medical care that your good doctors sell you. They teach the medical student, the intern, the resident, the graduate fellow and the postgraduate physician. They give the lectures at medical-society meetings and write the articles in medical journals. They determine the quality and the nature of the medicine of tomorrow. In doing this they are the best salesmen of pharmaceutical products. And while doing this they are personally giving all of us, day and night, the special care that they, through this institution, are particularly equipped to give.

What is the public's and industry's and your appraisal of the worth of such service? Compare the salaries and equipment of hospitals with those of industry serving society by developments pertaining to automobiles, airplanes, agricultural implements, radios, rubber, plastics and chemotherapeutic agents. Salaries of $2,000 to $4,500 are usually paid clinical investigators. The provision of more is difficult. Moreover, appointment is usually on a short-term basis, and too frequently a salary is dependent on a year's grant whose renewal may not be determined until two weeks before its expiration date. There are several men in this room whose contributions to medical knowledge have made them known in every country in the world that enjoys the benefit of modern medical science. They get just such salaries. The technical workers in clinical laboratories — college graduates and highly skilled persons — fare no better, receiving salaries of from $1,500 to $2,000 as compared with the $2,000 to $3,000 available to them in industry. Yet clinical research depends in no little degree on the quality of their work. And the quality of medical care depends more and more on the information that such technicians give physicians or surgeons concerning the composition of the blood, its type, the micro-organism that is involved or the tumor that is or is not malignant. One wonders if the pharmaceutical companies are wise in putting more money into advertising than into the hospitals that introduce their products and educate doctors in their use.

Is it because the charity tradition still pervades the public's concept of the large teaching urban hospital that the public, in making payments under hospital and medical-insurance plans, does not pay costs and thus still leaves much to charity? Does that tradition, as well as the educational character of these hospitals, encourage sentimental support rather than a realistic and material purchase of the concrete services rendered? We speak of supporting hospitals but not of supporting industries. Each of us buys what he gets. Perhaps the inadequate support of hospitals reflects the thought that medicine is concerned with lessening illness rather than producing health — the value of the institution, therefore, being conceived of in negative rather than positive terms. Yet people spend literally billions on doctors and pills. Medicine is, I believe, the third largest business in terms of money spent. But the teaching hospital, which determines in no small way the quality and improvement in medical care, is faced with possible bankruptcy. A past president of the American Hospital Association, who knows hospitals, remarked at a meeting a few months ago that there were probably only a dozen hospitals in the United States that would avoid insolvency in the next few years unless there is a drastic change in hospital financing. If the public does not finance the difference in the cost of medical care given by such institutions as this and that given by the smaller hospital, how can the teaching hospital continue to provide the difficult medical care for which doctors refer patients to obtain the treatment that is not available elsewhere? It is that type of care that makes the value of this institution, both to the patients who come here and to all those who never come here but who benefit by the doctors, nurses, social workers, dietitians and technicians who are educated here. It is the new, the carefully controlled and the well defined therapy that such hospitals as this provide that makes them of value to industry.

They could be made of far more value. The most effective utilization of a therapeutic agent demands at least a knowledge of its absorption and distribution within the body, of its excretion and degradation and of its toxicity and therapeutic effectiveness in relation to concentration in body fluids and tissues. This information has been obtained for only a few of all the many therapeutic compounds used today. One may well ask if we are administering such generally used substances as the barbiturates, hydantoinates and digitalis preparations to no better advantage than we used quinine and quinacrine prior to the recent studies conducted under the direction of the Board for Co-ordination of Malaria Studies of the Office of

Scientific Research and Development — studies that systematically defined the efficient use, in the control and cure of malaria, of both the heretofore empirically used agents and the new and superior synthetic antimalarial drugs developed under this effectively planned and executed research program.

The experience obtained during these studies demonstrated again that the optimal utilization of medication in man can be defined only through clinical testing. The behavior of these drugs in the human being could not be predicted reliably from studies on animals other than the monkey. The same reservation is true of operating procedures. These studies also demonstrated the limitation even of the monkey owing to the difference between its susceptibility to disease and man's and to the difficulty of producing in the monkey the conditions simulating those demanding operative therapy in man. This does not mean that patients are used as guinea pigs. It means that teaching hospitals can give patients newer and more effective therapy than can be obtained elsewhere. Incidentally, it does not mean that as much information as possible should not be obtained on mice, rats, chicks, ducks, guinea pigs and other animals before studies are undertaken with the monkey. Only in that manner will the difficult and expensive monkey experiments be efficiently conducted, and will all the information be obtained that makes utilization of new drugs and operative procedure in man safe.

In this connection it may be remarked that the antivivisectionist is one of the few people who eat their cake and have it too. So long as he is unsuccessful in prohibiting such clinical investigation, he may safely indulge in denouncing that by which he happily benefits. For no doctor will give him a drug or subject him to an operation that has not been tried and perfected by experimentation.

Such development of new and better therapy is expensive. The O.S.R.D. studies on malaria therapy for two and a half years cost the Government some $5,500,000. The clinical testing conducted by this hospital, which was one of five clinical testing units under the program, cost $220,000. The total cost of the clinical testing probably approximated $1,500,000. Yet had the war in the East lasted another year the reduction in the drug bill alone from the use of the new compounds instead of quinine and quinacrine would have paid for the studies. As it is, this saving will be realized by society in general, and a substantial profit will accrue to at least one pharmaceutical company.

The opportunity of similarly improving and developing therapy in other fields is wide open. The field can best be cultivated not by collective farming but by the group services of teaching hospitals.

The effective utilization of these group services can be increased in other ways. For example, a paying patient rarely obtains the medical care that these group services are particularly qualified to give unless he is admitted to a hospital and occupies a hospital bed. Frequently this is unnecessarily confining and expensive and may deprive some other patient of the bed he really needs. The Mayo Clinic is, I believe, one of the few group practices that is equipped to make its hospital staff and laboratory facilities available to ambulatory patients.

One other consideration deserves mention because it may affect the future of the group services of teaching hospitals that — I hope we all agree — are fundamental to the improvement of medical care. If the current extension of medical, as differentiated from hospital, insurance is successful enough under either private or legislative plans to prevent illness itself from resulting in medical indigence, the services of the highly trained and integrated group practices of teaching hospitals may be curtailed. The patient who has heretofore come to the wards of such hospitals may for better or for worse elect to be cared for by an individual physician in either a teaching or a nonteaching hospital. The problem that this presents is not dependent on the extension of governmental insurance. As a matter of fact, the legislative proposals, except so far as they may be more successful in covering more people, present less threat in this respect than the voluntary schemes. They permit the patient free choice of a physician, groups of physicians or hospitals, whereas the voluntary schemes provide for free choice only of a physician. The legislative proposals also make provision for financing medical teaching and research. The voluntary plans do not.

Such a possible effect of extension of medical insurance does not indicate, I trust, that indigence must be perpetuated in the interest of improving medical care. It does mean, however, that, if the group services of teaching hospitals are to weather the critical years ahead, they must be strengthened by increasing the public's understanding and appreciation of the services they render. It means that we must, in a business-like manner, assure payment for the benefits society receives. Let us consider the means of doing these things without prejudice and in the light of what is best for the public as a whole solve the problems and take advantage of the opportunities to develop the teaching general hospital to its full potentialities.

ACUTE YELLOW ATROPHY FOLLOWING CINCHOPHEN ADMINISTRATION*

Report of a Case

ALFRED R. LENZNER, M.D.,† L. MAXWELL LOCKIE, M.D.,‡ AND CHARLES F. BECKER, M.D.§

BUFFALO, NEW YORK

ABOUT twenty years ago Cabot[1] first reported a case of acute yellow atrophy allegedly due to cinchophen. Although similar cases have been recognized since that time, clinicians who use cinchophen with no observed untoward effects have minimized it as a hepatotoxic agent. One series has been reported, for example, in which cinchophen was given to 2500 patients without a fatal case.[2]

The toxic manifestations of cinchophen against which the physician is usually cautioned are chiefly those of the skin. Among them, urticaria and the erythematous morbilliform rashes are said to be most frequently encountered. But perhaps more important are signs indicative of hepatic damage. These include nausea, emesis, dark urine, icterus and discomfort in the right upper quadrant. With these symptoms the dermatologic complaint is, unfortunately, an infrequent one.

The following case of acute yellow atrophy terminated fatally twelve days after the ingestion of 2 gm. of cinchophen.

A 59-year-old Jewish housewife was admitted to the surgical service of Dr. Herbert A. Smith with the chief complaints of painless progressive jaundice, anorexia and nausea of 6 days' duration. The first symptoms had been extreme anorexia and nausea, without emesis or abdominal discomfort. These were accompanied by jaundice and dark urine, both of which had deepened rapidly. Two days after the onset of these initial symptoms, an attempted gall-bladder visualization had failed. Fluoroscopy with roentgenograms had disclosed no abnormalities of the esophagus, stomach, duodenum or abdomen. Continued nausea had prevented food intake of any consequence almost from the onset. Listlessness had progressed to drowsiness, and fleeting episodes of disorientation had become evident on the day preceding admission.

The patient had seen a physician for a long-standing arthritis of the ankles. She had taken a total of 2 gm. of cinchophen on the day preceding the onset of the initial symptoms. So far as could be determined from her physicians and family, cinchophen had not been given previously.

The past history revealed that during the preceding 4 years the patient had been receiving salicylates and injections of vaccine, as well as physiotherapy for the ankles. These measures had been instituted by several physicians for rheumatoid arthritis. She had always been ambulatory. Since for 1 year before admission she had experienced mild postprandial eructations and because of obesity, fatty foods had been eliminated from the diet. The eructations had been relieved, and the weight remained constant. There had been no change in bowel habits. Twenty-three years previously, vaginal hysterectomy had been performed under ether anesthesia for a fibroid uterus. There was no history of previous icterus or of transfusions.

Physical examination at the time of admission disclosed a moderately obese, somewhat disoriented woman with a deeply bronzed icterus. The pupils were regular, equal and normally reactive; neurologic survey revealed no abnormalities. There were no tophi. The tongue was somewhat dry, and the mucous membranes icteric. The heart and lungs were not remarkable. Neither the liver nor the spleen was palpable or tender. Rectal examination was negative. Rheumatoid arthritis of the ankles was present. The blood pressure was 150/80; the temperature, pulse and respirations were normal.

The results of certain laboratory procedures are presented in Table 1. The serum alkaline phosphatase was 7.3 Bodansky units per 100 cc. A cephalin flocculation test was ++++, and the prothrombin time, 30 seconds (normal, 16 seconds). Urinalysis revealed a few red and white cells, a positive test for bile in a dilution of 1:100 and a specific gravity of 1.014; there was no albumin on admission, but a + test was obtained on the following day. The stool was tan gray. The blood film showed a uniformly, mildly macrocytic picture. Examination of the blood revealed a red-cell count of 4,500,000, with 13.5 gm. of hemoglobin (photometric — normal, 14.4 gm.). The hematocrit reading was 49 on the same sample of blood. The mean corpuscular volume of the erythrocytes, therefore, was 109 cubic microns. The white-cell count was 7000 on admission, and 17,000 on the fourth hospital day; 70 per cent of the leukocytes were neutrophils.

The course was rapidly downhill. Drowsiness and disorientation progressed to semicoma by the 2nd hospital day. Severe, irreversible hepatic damage was present, as evidenced by the cholemic state and by a definite decrease in the size of the liver to percussion on successive examinations. The plasma prothrombin time remained elevated to 30 seconds even after the administration of menadione bisulfite. No ecchymoses were observed at any time.

It was decided to give a massive dose of methionine intravenously. Accordingly, 15 gm. of crystalline *d-l* methionine (0.25 gm. per kilogram of body weight) was dissolved by boiling in 500 cc. of a 10 per cent solution of casein hydrolysate. This was infused without reaction over a period of 4 hours. The natural course of the disease progressed unaltered, however. Despite adequate parenteral fluids, oliguria was noted on the following day. Coma deepened, and the atmosphere in the patient's room soon became permeated with a peculiar, musty odor, not unlike that of the infused methionine solution. Signs of free peritoneal fluid developed, in addition to those of bronchopneumonia, and the patient died on the 4th hospital day — 12 days after the jaundice and dark urine had first been noticed.

Autopsy. The body was that of a moderately proportioned woman measuring 147 cm. in length. The integument and conjunctivas exhibited deep icterus. There was no peripheral edema. Exposure of the peritoneal cavity revealed 1500 cc. of brown-yellow ascitic fluid. An unusually atrophic liver (Fig. 1) lay considerably recessed beneath the right costal margin. Its surface was irregular, with low, plateau-like, tawny-brown elevations separated by rather extensive, irregularly shaped, depressed deep-red areas. The organ weighed 650 gm. (normal weight, 1200 to 1400 gm.).

The cut surface of the liver presented a striking picture. Only a few portions of the parenchyma remained intact. The largest sections, which were situated chiefly in the superior portion of the right lobe beneath the capsule and also in the caudate lobe, varied in size from that of a large cherry to that of a walnut. In the left lobe there were a few much smaller remnants varying from match-head to pea size. All these remnants were grossly green yellow, suggesting icterus and considerable fatty change. There were no structures that could be interpreted grossly as nodular regenerates. The intervening tissue, which com-

*From the University of Buffalo School of Medicine and the Buffalo General Hospital.

†Resident in medicine, Buffalo General Hospital.

‡Professor of therapeutics, University of Buffalo School of Medicine; junior assistant attending physician, Buffalo General Hospital.

§Associate in pathology, University of Buffalo School of Medicine; assistant pathologist, Buffalo General Hospital.

prised the bulk of the cut surface, was frankly red and of a distinctly soft consistence. Close scrutiny of these areas revealed a completely collapsed and considerably disintegrated architecture of the liver lobules. The entire gross picture, therefore, was interpreted as showing a marked degree of acute atrophy of the liver in what might be termed a predominantly "red" rather than a "yellow" state.

The histologic picture, as revealed in several different sections, showed extensive liver damage of a decidedly acute nature (Fig. 2). There were marked necrosis and destruction of the liver-cord cells and, over large areas, complete collapse of the normal architecture. In these collapsed areas the lobular pattern had entirely vanished; there remained only scattered regressive liver cells singly and in disjointed groups within the condensed and inflamed stroma (Fig. 3). Many of the necrotic and necrobiotic liver cells contained a great deal of fine, granular, golden pigment, apparently bilirubin or lipofuscin. In addition, there was distinct proliferation of the bile ducts, as well as considerable swelling of fixed tissue cells. Numerous lipoid-laden histiocytes were found, and there was much acute inflammatory infiltration, particularly in the periportal areas. Many bile canaliculi and a few smaller bile ducts were distended with bile thrombi. Other small bile ducts contained neutrophilic exudate within their lumens. In the more severely damaged areas there remained only small isolated groups of apparently undamaged liver cords. Finally, the preserved areas described grossly revealed fair-sized, intact remnants of liver parenchyma. Here, there was considerable edema of the intervening sinusoids, which were exceedingly dilated and filled with granular detritus. The liver cells, although intact, showed distinct regressive changes, with vacuolization and granularity of the cytoplasm. Here, too, were occasional necrobiotic and necrotic parenchymatous cells, whereas the bile canaliculi showed numerous bile thrombi. The over-all histologic picture was that of a severe degree of acute toxic necrosis, such as that seen in acute yellow atrophy.

The gall bladder was of normal size and thin walled and contained no calculi. Its fundus protruded almost 4 cm. beyond the upper edge of the markedly atrophic liver. The extrahepatic biliary passages were collapsed and contained only a slight amount of thin yellow bile.

The spleen was of average size, weighing 160 gm., and was grossly not remarkable. Microscopically there was marked atrophy of the malpighian follicles. There was also considerable congestion of the red pulp with dilatation of the sinusoids, which contained moderate numbers of leukocytes and plasma cells, in addition to erythrocytes. The reticulum was slightly increased.

The kidneys were of average size, with thin, easily removable capsules. Aside from minimal persistence of embryonal lobulation they presented only slight diffuse, fine granular scarring of the cortices. On section the parenchyma revealed distinct icterus, a regular corticomedullary junction and a cortex of about 7 mm. in thickness. The major renal vessels, the pelves and the ureters were not remarkable. The urinary bladder was completely contracted and contained only a few drops of urine.

Microscopical sections of the kidneys revealed interesting findings. Aside from a rare hyalinized glomerulus, the renal corpuscles were entirely intact. Occasionally, the glomerular spaces were slightly dilated and contained droplets of deep-pink-staining material.

The tubular system, however, showed severe alterations.

TABLE 1. *Significant Laboratory Data.*

DATE	FASTING BLOOD GLUCOSE	BLOOD UREA NITROGEN	SERUM PHOSPHORUS	SERUM BILIRUBIN	TOTAL PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc*
1/26/45	56	11	—	19.2	6.1	—	—
1/27/45	86	—	3.4	—	5.1	2.4	2.7
1/29/45	62	15	4.8	25.0	6.1	2.8	3.3

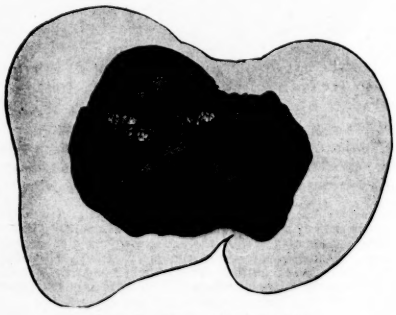

FIGURE 1. *Photograph of the Liver.*
The outline indicates the size of a normal liver.

FIGURE 2. *Photomicrograph of the Liver.*
This shows a remnant of parenchyma with marked inflammatory reaction in the periportal stroma and proliferation of the bile ducts.

The proximal convolutions exhibited marked albuminous degeneration with a great deal of desquamated detritus and droplets of deep-pink-staining material within the lumen.

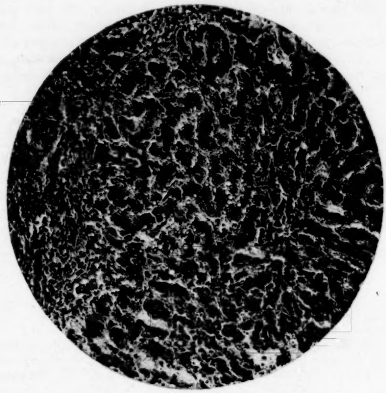

FIGURE 3. *Photomicrograph of the Liver.*
In the remnant of parenchyma there are regressive changes and vacuolization in the cytoplasm of the liver cells, as well as an inflammatory reaction in the sinusoids and the periportal stroma.

Most of the thin segments were dilated and empty, but a few contained red-pink-staining casts. The ascending limbs of Henle's loops occasionally contained similar casts, and

FIGURE 4. *Photomicrograph of a Kidney.*
Note the dilatation of a distal convoluted tubule, with bile cylinders and mononuclear cells within the lumen.

rarely a bile cylinder. Bile casts, which were more frequent in the distal convolutions, were rarely associated with 1 or 2 mononuclear cells within the lumen (Fig. 4). In several distal convoluted tubules a dark-blue granular substance appeared. Occasionally, cystic structures were seen — possibly distal convolutions or collecting ducts — lined by flattened epithelium. These contained a similar dark-blue granular substance.

Perhaps most interesting were the lesions in the collecting tubules. The peripheral branchings of the collecting ducts showed rather distinctly dilated lumens with numerous bile cylinders. Many of the collecting tubules in the centrifugal portions of the medullary rays contained considerable amounts of a peculiar, amorphous, granular material similar to that noted in the distal convolutions. This substance, taking a dark bluish-purple color in a hematoxylin-eosin preparation, gave a positive reaction with the von Kossa stain for calcium (Fig. 5). With this technic it was apparent that although the bulk of this material lay within the lumen, small amounts were deposited in the cytoplasm of the tubular epithelium as well.

The small capillary vessels of the kidneys showed intense hyperemia, especially in the pyramids. The small arteries revealed moderate sclerotic thickening.

Both lower lobes of the lungs grossly showed distinct flaccid atelectasis, with slight to moderate, apparently in-

FIGURE 5. *Photomicrograph of a Kidney.*
This section shows deposits of calcium in the collecting tubules of the medullary rays (von Kossa stain).

flammatory, edema of the atelectatic parenchyma. Histologic sections showed marked signs of recent pneumonia.

The heart was of normal size and grossly revealed entirely normal chambers, valves and coronary arteries. Histologically, the myocardium showed only slight interstitial edema, with scattered plasma cells and leukocytes, and distinct cloudy swelling of the myocardial bundles.

All other organs, including the pancreas and the thyroid, parathyroid and adrenal glands, were normal. Permission was not granted for examination of the brain.

The findings in the liver in this case correspond well with the classic pathological picture of an acute toxic necrosis. That the disease was of a fulminating character clinically is amply shown pathologically by the severity of parenchymatous damage, the acute inflammatory response and the absence of regeneration or of reactive fibrosis. Reichle,[3] in a review of 7 reported cases of death due to cinchophen, to which he added 2 cases of his own, — in

all of which autopsy was performed, — noted in every case that there was evidence of a "hepatitis" or of a "degeneration" of the parenchyma of the liver. Each of his own cases exhibited a toxic cirrhosis after a terminal hepatic illness of several weeks' duration.

It is of interest to compare certain of the histologic findings in the case presented above with those observed by Lucké[4] in his study of fatal epidemic hepatitis. In our case, in which there was no appreciable zonal pattern of destruction in the liver lobule, such as that described in epidemic hepatitis, the agent apparently attacked all regions within the lobule with equal severity, producing all stages of cellular disintegration — fatty changes, vacuolization and coagulation of cytoplasm — and cellular death. This pattern of necrobiosis and necrosis, in itself, also differs from that observed in fatal epidemic hepatitis, in which rapidity and completeness of cell destruction are distinguishing features.[4] In the regions still intact, however, the inflammatory infiltration was more marked in the periportal areas, consisting largely of neutrophils.

We observed no endophlebitis of the central veins. Nor was there any recognizable persistence of the outline, by small proliferating bile ducts, of the completely destroyed lobules. Both features were described in epidemic hepatitis. A characteristic of acute yellow atrophy that was well shown in this case was the extraordinarily rapid disappearance of many of the damaged liver cells. Lucké, also noting this phenomenon in his material, assumed that the necrotic cells had been swept away by enzymatic action. The tempo of the disease in our patient was apparently of such rapidity as to preclude the development of nodular regenerates.

Recently, studies on acute or fulminant epidemic hepatitis running a fatal course in ten days or less have appeared.[5, 6] In most cases the liver presented a moderate reduction in size, with a smooth or occasionally finely wrinkled surface. Nodular regeneration, prominent in the subacute form of this disease, was absent or minimal. Microscopically, extensive destruction of liver cells dominated, usually involving uniformly all parts of the liver. Apparently, this occurred initially in the central zones of the lobule. Even in cases with a clinical history of brief duration, cell destruction was often far advanced, and complete lobules had been swept away. Inflammatory reaction, most conspicuous at the lobular periphery, was severer than that in the subacute form of the disease.

The case presented above, however, differs in certain respects from fulminant epidemic hepatitis, notably in the size and shape of the liver, the gross appearance of the cut surface and certain microscopical findings, such as the presence of stages of cellular degeneration and the absence of zonal patterns of disintegration.

So far as the cause of the hepatic damage is concerned, can the administration of cinchophen be considered merely an unfortunate coincidence? The report by Palmer and Woodall[7] of 88 deaths in 191 recorded cases of hepatitis associated with cinchophen seems sufficient clinical proof for the hepatotoxic potentialities of this drug in the susceptible patient. MacBryde[8] states that a number of cases of toxic hepatitis consequent to cinchophen undoubtedly have been mislabeled acute infectious hepatitis. Frequently, as in the case presented above, a history of cinchophen ingestion is not elicited at the initial inquiry.

It has been observed that cholemic nephrosis has received much less attention than the condition merits.[4] Fahr[9] described the findings in cholemic nephrosis in some detail in 1925. Ayer's[10] pathological analysis of renal lesions in 18 infants who were jaundiced from congenital biliary atresia is perhaps more comprehensive than any written about this lesion. He consistently found pigmented bile casts in the distal convoluted and collecting tubules in his cases.

In a subsequent study of post-transfusion uremia, Ayer and Gauld[11] concluded that the essential features of the renal lesions following fatal transfusion reactions were similar to those seen in the kidneys of infants with biliary atresia. The findings in the kidneys of patients succumbing to subacute epidemic hepatitis also correspond to those described by Ayer.

The tubular lesions seen in our patient also closely paralleled those reported by Ayer in jaundiced infants. Not heretofore described, however, in the nephroses accompanying acute yellow atrophy, acute or subacute epidemic hepatitis, obstructive jaundice or post-transfusion uremia is the presence of a considerable amount of calcium in the cortical collecting tubules and their peripheral branchings and also within occasional distal convolutions. Flocks[12] recently reported asymptomatic pelvic and intrarenal calcium urolithiasis in its early stages. Although its exact intrarenal location is not described, — except within the tubules, — it is presumably located within the collecting tubules and ducts of Bellini in the pyramids. Flocks termed the substance a "phosphate."

What is the mechanism of this calcium precipitation? Several possible causes can be excluded. So far as we were able to determine, the patient had never taken irradiated ergosterol. Except for short periods she had been ambulatory, hypercalcinuria due to osteoporosis from immobilization being thus eliminated. At autopsy the parathyroid glands were not conspicuous, nor were there any evidences of multiple myeloma. Urinary stasis, infection and heavy metal intoxication were also absent.

It seems, then, that few possibilities remain. So far as we know, the infused methionine solution did not contain significant amounts of calcium salts.

Unfortunately, however, a blood calcium determination was not made. We are unable to say whether or not the amino acid itself produced precipitation of the calcium salts, or even tubular necrosis.

The renal picture was interesting because of its clinicopathological correlation. The bladder was empty at post-mortem examination, despite ample fluid therapy. In spite of this anuria, however, the terminal blood urea nitrogen was 15 mg. per 100 cc. With severe hepatic dysfunction producing a decrease in urea formation, this figure probably falsely implies normal renal function. In view of a urea nitrogen value of 11 mg. three days previously and adequate parenteral fluids in the interim, it may have indicated early renal retention. A phosphorus determination in this particular case is more significant, for urea and creatinine figures probably mean little. Indeed, a significant rise of the serum phosphorus did occur concomitant with the development of anuria.

Urinary suppression was not present in Wilbur's[18] cases of bile nephrosis. Nor was there clinical evidence of renal insufficiency in Ayer's[10] infants with congenital biliary atresia. Although clinical renal failure was apparent in Ayer and Gauld's[11] cases of post-transfusion uremia, the morphologic alterations were essentially similar to those seen in the jaundiced infants. It was therefore considered unlikely that the morphologic changes in the kidneys after delayed reaction to transfusion were responsible for the renal failure observed clinically.

In the case presented above, however, the pattern of the kidney lesions seems significant. The calcium was present in considerable amounts in numerous tubules. The bile cylinders were situated proximal to the precipitated calcium. Furthermore, the tubular system proximal to the segments impregnated with calcium showed dilatation, whereas distally there was none. Histologically, therefore, there seems to have been evidence for an obstructive factor in the anuria in this case.

* * *

In their search for criteria for the safe administration of cinchophen, Palmer and Woodall[7] were forced to admit the absolute unpredictability of its action. They found no method of administration that ensured against a fatal result. Previous ingestion, the absence of a history of allergy, the age and sex of the patient and even the dose seem to be irrelevant. In our case, for example, there was no post-mortem evidence, such as hepatic regenerates, cirrhosis or splenic enlargement, of pre-existing hepatic disease. This evidence is important, for it rules against lowered hepatic reserve from previous liver disease, although it cannot exclude possible sensitization due to previous ingestion of cinchophen.

We have personal knowledge of at least 2 patients who developed urticaria following the ingestion of a single tablet of cinchophen. Short and Bauer,[14] influenced by a study of 41 cases, considered this urticarial reaction an absolute contraindication to further cinchophen administration. Fink and Gay[15] reported cases of urticarial rashes as long as three months after the discontinuation of atophan.

The usage of cinchophen is no longer widespread. If it must be employed, it should probably be reserved for the patient with severe gouty arthritis, especially in the interval between the acute attacks. Colchicine remains the drug of choice for the acute attack of gouty arthritis.

Our case of acute yellow atrophy beginning on the day after the ingestion of 2 gm. of cinchophen terminated fatally twelve days later. The gross and histologic findings in the liver differed in some respects from those reported in cases of acute or fulminating hepatitis. Clinical and pathological evidence of pre-existing hepatic disease was absent. Urinary suppression and early phosphorus retention were featured. In addition to the usual picture of cholemic nephrosis, the kidneys showed considerable amounts of calcium within the collecting tubules and their peripheral branchings.

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LEUKEMIA CUTIS*

Report of a Case, with a Discussion of Treatment by the Use of Hormones

WILLIAM H. ROBEY, M.D.,† AND G. GARDINER RUSSELL, M.D.‡

BOSTON, MASSACHUSETTS, AND HARTFORD, CONNECTICUT

LEUKEMIA is characterized by hyperplasia of the leukopoietic tissues throughout the body and is usually associated with qualitative and quantitative variations in the circulating leukocytes. Urticaria, pruritus and prurigo, hematomas and actual tumor formations may occur. In the case reported below, the intense skin involvement began early; the leonine appearance of the face and general leukemic infiltration of the skin led to the diagnosis of leukemia cutis — a rare manifestation, only 4 cases having been seen at the Boston City Hospital in twenty years. In association with these skin lesions the blood may remain normal for years or may show only slight changes. Two biopsies early in the disease showed the leukemic lymphocytic infiltration of the lesions.

The case is reported because of its rarity and the effect of hormones on the subjective and objective symptoms.

C. W. P., a 51-year-old married business executive, had always enjoyed perfect health; his habits were excellent, and he kept good hours and used alcohol and tobacco in great moderation.

Late in March, 1942, a slight rash appeared, first on the chest and then on the upper back. No discomfort was felt, nor was there any indisposition. Two or three weeks later, a mild itching developed, increasing sufficiently to interfere with sleep. Gradually, the pin-point spots became confluent, emerging into larger and larger areas until the whole trunk took on the appearance of a mild sunburn. About the middle of June, there was a sharp attack of diarrhea of approximately 12 hours' duration that the patient attributed to food poisoning. A day or so later he noticed a slight swelling of some of the superficial lymph nodes and consulted one of us (G. G. R.).

The itching, especially at night, was increasing but not enough to interfere with the patient's daily activities. The lymph nodes seemed to subside, and there was little change for several weeks. On July 26, the patient played two rounds of golf, which he thoroughly enjoyed, and did not feel fatigued. Two days later, however, he was rather stiff and concluded that his game had brought into play some muscles not recently used. On the following day there was some swelling of the lymph nodes in the groins and axillas. His physician then made a complete physical examination that was stated to be negative, except for the skin and lymph nodes.

Three days later the nodes had increased in size, and the color of the skin had deepened. On August 3 a biopsy was performed, and 6 days later the patient was admitted to the Thorndike Memorial Laboratory, Boston City Hospital, where these clinical findings were confirmed by Drs. W. B. Castle and T. H. Ham. Of particular interest were the raised, ridge-like and hyperkeratotic plaques and the enlargement of the lymph nodes in the submental, cervical, axillary and inguinal areas. The nodes were approximately 1 cm. in diameter, elastic, movable and only occasionally slightly tender. There was doubt about enlargement of the spleen.

Examination of the blood on several occasions disclosed a white-cell count of 9000 to 9600, with 36 per cent adult and 5 per cent band neutrophils, 1 per cent eosinophils, 22 per cent small, 19 per cent large, 8 per cent young and 6 per cent atypical lymphocytes and 3 per cent adult monocytes. The red-cell count was 4,600,000, and on a smear the red cells and platelets appeared normal. The small, young and abnormal lymphocytes had nucleoli, but the cytoplasm did not appear immature. The sedimentation rate was normal, as was an x-ray film of the chest.

The most important diagnostic problem was the interpretation of the biopsy. Dr. Frederic Parker, Jr., did not come to a conclusion on the skin biopsy but made the following comment on that of the lymph node:

> The lymph node shows a loss of normal structure for the most part. It is diffusely infiltrated with what appear to be adult lymphocytes. The infiltration also extends into the surrounding tissues. Mitotic figures are fairly numerous. The most probable diagnosis seems to be lymphocytoma, which is consistent with lymphatic leukemia in either the aleukemic or the leukemic phase.

The diagnoses considered were leukemia cutis, Hodgkin's disease of the skin and mycosis fungoides in an early stage. Everything, however, seemed to point to one diagnosis: lymphatic leukemia of the skin, with diffuse erythematous thickening and pruritus, enlargement of the lymph nodes and moderate alteration of the differential count of the blood. A hope was expressed that the course of the disease would be sufficiently slow to permit reasonable comfort and the ability to work.

The proposed treatment consisted of x-radiation of the skin and lymph nodes and the use of Navitol as well as sunlight. Since it was known that some of these cases have been aided greatly by massive doses, the patient was given initially 20 drops of Navitol three times a day and finally 120 drops a day. It was suggested that this treatment be given a trial of from 6 weeks to 3 months with the hope of less itching and possibly some clearing of the lesions. If the Navitol did not help, it might be discontinued and given a retrial after a month. Sunlight was to be tried over one area, namely the back, in direct exposure for 10 minutes, the time being increased 5 minutes every other day until there was an opportunity to observe if the area tanned and if the itching was relieved.

On September 29, the patient had taken Navitol in full dosage for 10 days. The skin was becoming a deeper red, more pruritic and in some areas more indurated. The superficial pelvic lymph nodes were more prominent, and a small amount of edema of the feet was observed. Examination of the blood revealed a red-cell count of 3,980,000, with a hemoglobin of 13 gm. (85 per cent), and a white-cell count of 20,450, with 17 per cent neutrophils, 81 per cent normal and abnormal lymphocytes and 2 per cent eosinophils; some of the lymphocytes appeared young. The skin discomfort was more intense. Small doses of Dilaudid probably lessened the itching somewhat and therefore diminished insomnia.

In spite of the x-ray therapy and the doses of Navitol, the patient's discomfort continued to mount; the itching became more constant and violent, the lymph nodes larger and the skin more indurated, and in addition the scrotum and penis were markedly edematous. It was decided to send the patient to the Memorial Hospital in New York City, where he was studied by Drs. C. P. Rhoads and L. F. Craver. The white-cell count at that time was 17,300, and a little later 20,450. The patient was in the Memorial Hospital from October 22 until November 6. At first he received total body irradiation in two small doses, and a single dose of 200 r was subsequently applied to each of the six external lymph-node groups.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Hartford Hospital.

†Clinical professor of medicine, emeritus, Harvard Medical School; consulting physician, Boston City Hospital.

‡Visiting physician, Hartford Hospital.

On November 20 the patient weighed 166 pounds — this fact is mentioned because of the marked variations in weight, depending on the induration of the skin and the intensity of the edema. The skin over almost all the body was described as a "horrible brownish red." The patient was more animated and was working a part of each day. There were some large nodes in the groins, smaller ones in the axillas and still smaller ones about the jaw and the posterior chain in the neck. The spleen and liver were not palpable. The leonine expression of the face was striking; the color of the skin was a magenta red, and one of the most distressing symptoms was the constant itching, which made it impossible to refrain from scratching the face and head, especially the ears, which were greatly enlarged.

Examination of the blood at that time revealed a red-cell count of 4,310,000, with a hemoglobin of 13 gm. (88 per cent), and a white-cell count of 20,600, with 9 per cent neutrophils (3 per cent myelocytes and other forms showing many toxic granules), 80 per cent lymphocytes (25 per cent large young forms and 55 per cent small forms) and 11 per cent smudges — probably lymphocytes. A subleukemic leukemia could not be excluded on this examination.

Navitol, which had been given daily in full doses of 150 drops, was discontinued, since it did not seem helpful and the patient thoroughly disliked it. The skin was much indurated, and the oozing from various areas required careful dressings each morning. No material change in the blood picture had occurred.

On January 30, 1943, the patient was seen in consultation by one of us (W. H. R.) at the Hartford Hospital. He was disoriented. The temperature was 103°F. The skin, even on the scalp, was a dusky red, and much of the hair had dropped out, leaving only small scattered tufts; the nails had degenerated. There were oozing areas in which the itching was intense. The patient was so ill that he was given oxygen inhalations.

The use of female hormones was suggested, and treatment with Progynon B was immediately started in increasing doses; all forms of x-ray therapy were stopped.

There was marked edema, which raised the body weight to a maximum of 220 pounds and was relieved to a slight degree by a mercupurin suppository. On February 6 the edema had largely disappeared. The chest had become clear, and oxygen had not been given for 5 days. The weight had dropped from 220 to 190 pounds. The inguinal and axillary lymph nodes seemed to be somewhat larger and harder. The liver and spleen could not be felt. The loss of edema was remarkable. Navitol had been stopped for a week, but Progynon had been continued.

At that time the main problem was respiratory. Greater difficulty in breathing and rales over the entire chest persisted for several days before x-ray examination was performed. The lungs showed congestive changes and patchy areas of increased density, without evidence of lymph-node enlargement, that were interpreted as being due to infiltration of the lung tissue and to edema similar to that in the skin. X-ray treatment was considered valueless, and for several days oxygen was again administered. The skin and subcutaneous tissue had become definitely less edematous. The temperature was moderately elevated — 101 to 102°F. It was thought that Progynon might be credited with the weight loss. The patient seemed more comfortable, but although lucid at times, he was often confused and did not remember anything about the previous consultation.

On March 11 examination of the blood showed a hemoglobin of 81 per cent and a white-cell count of 28,100, with 31 per cent neutrophils, 65 per cent lymphocytes, 3 per cent eosinophils and 1 per cent monocytes. Ten per cent of the lymphocytes were young forms. The skin was continually desquamated and itchy. The circulation seemed adequate, and the urine was normal.

On March 25 diethylstilbestrol was added — in doses of 0.5 mg. at first and subsequently 1 mg. three times daily; the Progynon was administered as previously. Obtundia ointment did more to relieve the itching than anything that had been tried. Early in May the whole condition showed improvement.

At the end of June the weight was 152 pounds, and the edema had practically disappeared except in the upper thighs; the scrotum was normal. The nails were growing, but the patchy baldness remained. There were some lymph nodes in the axillas and thighs. The liver was much smaller. The skin over the entire body had become lighter in color. The breasts were slightly conical, and for that reason the dose of stilbestrol was reduced by half.

The hemoglobin was 11.7 gm. (75 per cent), and the white-cell count 4200. A blood smear showed few white cells; the red cells approached normal in appearance. The platelets were small but numerous. In the stained specimen no abnormal cells were seen. The patient was anxious to be out and about, but since the thighs and legs were still large and heavy, walking was laborious.

On September 14, after making a motor trip of 120 miles, the patient arrived at his destination without undue fatigue, and his whole appearance was almost incredibly normal and healthy. The skin was clear and smooth, the hair had grown, and the appetite was excellent. Except for slight swelling about the ankles there was nothing unusual in his appearance.

In October the patient had recovered sufficiently to resume business on a half-day basis; he played eighteen holes of golf with ease, and his spirits were high. Stilbestrol had been discontinued for about 4 months, but Progynon had been taken, with a steady improvement in vigor and appearance. His condition was so satisfactory, even to complete freedom from desquamation in the legs and feet, that Progynon was stopped 3 months later.

On January 14, 1944, the patient developed a fine petechial rash over the chest and shoulders that was quite different from the original smooth erythema observed the year before. Although the hormones had not been given except in small doses for several weeks, the condition remained much improved, and the rash diminished after the Progynon was resumed in full doses. The blood picture was normal. A few young white cells were seen. On February 17 the patient saw Dr. Craver, who considered the results in this case remarkable and who stated that resumption of Progynon was indicated in view of the reappearance of erythema in patches since its discontinuance.

On March 21 the condition was worse, the rash was confluent and the skin indurated.

In June, after a long course with Progynon, diethylstilbestrol and vitamins, the weight, which had risen in the preceding months, was reduced to 170 pounds, remaining at that level. There was little tendency to purpura, and the exudation was limited to the feet. The patient was considered definitely improved.

The rash seemed to be influenced by Progynon, for the petechial character became less marked and less brilliant. Since the rash seemed to the dermatologist and to the patient's own physician to be of quite a different character from that of the original, it was the desire of the dermatologist to discontinue the hormones for a time to see what effect purely local treatment would have. In July, however, the lymph nodes became larger, and the induration of the skin more marked. The edema and oozing increased. With all these changes the blood picture remained essentially the same. On September 6 another consultation took place while the patient was still at home. He was a dark red oozing mass, itching constantly and generally miserable. Three days later he was sent to the Hartford Hospital, where, on September 14, he died suddenly before the resident could reach his room. The manner of death suggested pulmonary embolus.

Autopsy. The anatomical diagnoses were chronic lymphatic leukemia, with leukemic infiltration of the spleen, liver, kidney and bone, leukemia cutis, thrombus in the right iliac vein, pulmonary embolus, with an infarct of the right lung, thrombus in the left renal vein and chronic cholecystitis with cholelithiasis.

The skin over the body showed a most remarkable appearance. Everywhere, from head to foot, it had a deep-red, scaly, thickened appearance. This was most prominent over the lower extremities, although it involved the upper chest, arms and face. On the lower extremities there were areas of ulceration between zones of thickened, scaly, red skin. These ulcerated areas, particularly those on the medial aspect, had a moist appearance. The skin on palpation had a brawny induration. The right leg was rather markedly edematous, and the left was atrophic in appearance. There was a moderate edema of the scrotum and penis. The skin was inelastic and thickened, and there was a diffuse edema of the subcutaneous fatty tissue; thin fluid exuded when the tissue was incised. The breasts appeared enlarged and when sectioned showed rather marked hypertrophy. The axillary lymph nodes were greatly enlarged, measuring up to 3 to 4 cm. in diameter; they were of a soft consistence and had a pink appearance.

Sections of the lymph nodes showed extensive destruction of the normal architecture by uniform infiltration of the dull appearing lymphocytes, typical of lymphatic leukemia.

Microscopical examination of the skin showed that the corium was extensively infiltrated by lymphocytes, a typical leukemic reaction. The remainder of the picture was consistent with lymphatic leukemia.

* * *

When this patient was seen at the Hartford Hospital in late January, 1943, he had a temperature of 103°F. and was disoriented; the eyes were the only recognizable feature, and the end seemed imminent. Since there was a chance that female hormones might be of value, other forms of treatment (Navitol and x-radiation) having been of no avail, Progynon was begun at once, and steady progress occurred until, in August, 1943, there remained only slight serous oozing about the ankles.

It may be argued that this case of leukemia cutis might have improved under some other treatment, or possibly with none. As a matter of fact, the symptoms diminished only with the use of hormones. If a similar case is seen, treatment with hormones certainly deserves serious consideration.

MEDICAL PROGRESS

EFFECTS OF PROTEIN DEFICIENCY ON THE PREGNANT WOMAN AND FETUS AND ON THE INFANT AND CHILD*

HAROLD C. STUART, M.D.†

BOSTON

MANY of the ill effects of a lack of sufficient or suitable proteins in the diet are encountered at all ages and in both pregnant and nonpregnant women. Some of them are particularly likely to occur during pregnancy, and others at certain periods of rapid growth in childhood when requirements are exceptionally high. The specific syndromes resulting from protein deficiency are not reviewed below, but attention is given to certain other effects that appear to be associated with pregnancy, with the health and development of the fetus, and with the progress of growth and development in infancy and childhood.

In the discussion of a single nutritional essential it must be kept in mind that except under conditions of rigid experimental control, attainable only in studies of animal nutrition, there are always many variables. For example, a diet low in protein is likely to be lacking in other essentials as well. Furthermore, the requirement for protein is modified by other characteristics of the diet. In some of the studies reviewed below the part played by protein is only implied, sometimes quite logically on the basis of all the known facts but at other times as a hypothesis to stimulate further study. For example, a woman who eats poorly and hence obtains too little protein may do so because of ignorance, disease or lack of money or because she is in a poor physical or psychologic state. Many other factors, therefore, must be considered, and supporting evidence is still required before one can conclude that protein per se is concerned with or primarily responsible for certain complications of pregnancy or conditions of infants at birth that have been found to occur much more frequently when the maternal diet has been poorly provided with protein than when liberally provided. Also, a child who is constitutionally inferior may grow or develop in an unsatisfactory manner, not primarily because he eats a generally poor diet or one lacking in protein but because constitutional inferiority contributes both to poor appetite and to poor progress in growth and development. Again, it may be difficult to establish whether or not the poor physical state and progress are related to a poor nutritional background, and if so, whether inadequate protein is the principal dietary factor involved.

PROTEIN DURING PREGNANCY AND LACTATION

Increased Requirements

Several nitrogen-balance studies[1–4] have shown that women normally store relatively large amounts of protein during pregnancy. This positive nitrogen balance, according to Wilson[5] and Macy and Hunscher,[6] begins about the tenth or twelfth week of gestation and increases to term. Part of the protein is needed for the development of new maternal tissues, such as the breasts and uterus, and part is utilized in building the tissues of the fetus, including the placenta and membranes, but the total stored is in excess of these needs. The average fetal body at the sixth lunar month has been found to contain only 8 gm. of nitrogen, whereas at term it contains 60 or 70 gm.[1, 2] The membranes and fluid at term contain about 19 gm., making a total for the mature ovum of 79 to 89 gm. An additional 17 gm. of nitrogen is required on the average for the development of the mammary glands and 39 gm. for the

*From the Department of Maternal and Child Health, Harvard School of Public Health.

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†Professor of maternal and child health, Harvard Medical School; head, Department of Maternal and Child Health, Harvard School of Public Health; physician, Children's and Infants' Hospital.

uterus,[5] making 56 gm. the amount needed on the average for the growth of maternal tissues. On the basis of these findings, it has been estimated that about 135 to 145 gm. of nitrogen beyond maintenance needs is required during pregnancy, or about 845 to 900 gm. of protein.[7] Macy and Hunscher[6] and Wilson[5] have shown that under favorable circumstances the amount of nitrogen actually stored is 200 to 400 gm., representing 1250 to 2500 gm. of protein, in excess of the probable utilization by the mother for herself and for the fetus in the replacement of old tissues or the construction of new.

A negative nitrogen balance sets in abruptly just before term,[6] and there is a substantial loss of nitrogen from the maternal organism during parturition and the post-partum period. For women who nurse their infants, there is an additional loss in the breast milk amounting to about 1 to 1.5 gm. of nitrogen a day, depending on the amount of milk secreted. Thus, it is usual to find a negative nitrogen balance throughout the puerperium, and often during the lactation period as well. The reserve of nitrogen stored during pregnancy, therefore, may be regarded as in part a natural mechanism to provide in advance for the large losses occurring during delivery and the puerperium, and in part for the high requirements of lactation.

The actual increase in dietary protein required to meet the needs of pregnancy is a matter of debate. From the calculations regarding nitrogen requirements discussed above and from studies by Burke et al.[8] of the condition of the infant at birth in relation to the level of maternal dietary protein, an increase in the protein of the diet during the last six months of pregnancy of 15 to 20 gm. a day above the woman's normal requirements may be assumed to be the average need.

If it is assumed that an allowance of 60 gm. of protein is desirable and adequate for the average nonpregnant woman and that an increase of 15 to 20 gm. daily is needed for these special purposes in pregnancy, the allowance recommended by the Food and Nutrition Board of the National Research Council[9] of 85 gm. during the latter part of pregnancy seems to be liberal and sufficient to take care of individual differences. Williams,[10] in a review of this subject, emphasized the important point that this figure presupposes a previously normal protein intake and nutritional state.

The question immediately arises of how nearly the diets of pregnant women approximate this allowance. Burke,[8] in studies at the Boston Lying-in Hospital, found that the diets in 68 per cent of 216 pregnant women contained less than 70 gm., those in 38 per cent, less than 55 gm. and those in 14 per cent, less than 45 gm. of protein daily. Arnell[11] in studies of 400 pregnant women in New Orleans found that 18 per cent took less than 42.5 gm. of protein daily — that is, less than half the allowance recommended by the National Research Council — and 79 per cent less than 70 gm. In dietary studies on 514 pregnant women in Philadelphia, Williams[12] found that only 13 per cent were taking 85 gm. of protein daily as recommended. Since many women habitually take a poorly balanced diet that is low in protein and do not change their habits appreciably during pregnancy, it is not surprising that the usual signs of protein malnutrition are encountered more frequently when the physiologic strain of pregnancy is superimposed on normal requirements.

The need for protein in the mother's diet during lactation has received considerable attention. In the dairy industry the value of a liberal intake of protein during the latter part of gestation for successful milk production has long been recognized.[13] In women, psychologic factors have such an important influence on milk production that the relation of diet and nutrition to milk supply is difficult to demonstrate. The evidence suggests that diet during pregnancy — and possibly before — has at least as much to do with a satisfactory supply of breast milk as the diet during lactation. Macy and her associates[14] have shown that a high-protein diet during the latter part of pregnancy is important for successful nursing, and that a diet high in animal protein results not only in the highest nitrogen retention but also in the highest milk yield.

Orr and Gilks[15] studied lactation and growth in a South African tribe that lived principally on cereals, roots and legumes and lacked milk and other suitable infant foods. The mothers in this tribe were unable to nurse their babies successfully for an average of more than three months, and after three months the infants grew poorly. In contrast, the mothers of a pastoral South African tribe, living mainly on animal foods, continued to nurse their babies successfully for long periods. The differences in size and physique of the infants of these two tribes became progressively more striking from three months onward.

Without going farther into the details of the controversial literature on the relation of diet and nutritional status to lactation, the following tentative generalizations seem to be justified. Women differ considerably in their capacity to develop breast tissue, and the development of the breasts during pregnancy may be further restricted by chronic malnutrition or by a lack of adequate protein. The quantity of milk that any woman secretes is determined only in part by breast development, for it is influenced by mechanical, psychologic and nutritional factors. Under favorable conditions a woman secretes milk at the expense first of the dietary protein and then of the protein tissues. She continues to do so for long periods, with a resultant negative nitrogen balance. How long or successfully she will secrete an adequate supply depends in part on the protein intake and nitrogen storage during pregnancy, as well as on the protein intake during

lactation. About one and a half times the amount of protein secreted in the milk is needed in the diet to provide for this — that is, about 25 to 30 gm. per liter of breast milk. The National Research Council's[9] recommended allowance for the lactation period is 100 gm. of protein daily — 40 gm. above that of the nonpregnant, nonlactating woman. This allowance seems to be liberal and sufficient to allow for individual differences in requirement and utilization. Various reports from famine areas indicate that when women are markedly underfed, they are unlikely to produce an adequate supply of breast milk. Protein deficiency appears to be an important factor, although probably not the only one involved in these situations. Garry and Wood[16] have suggested that the negative nitrogen balance frequently encountered in lactation may be conditioned by an energy intake too low for all the demands made on the lactating woman. Since the caloric requirement is markedly increased during lactation, it is clear that calories as well as protein must be considered. The successful nursing mother has been shown by Kaucher[17] to select usually a high-protein, high-calorie diet. Emotional instability is likely to affect the appetite adversely and is detrimental to successful nursing.

On the basis of these considerations, it seems to be important that a woman end pregnancy with liberal stores of nitrogen, and that she consume in the neighborhood of 2 gm. of protein per kilogram of body weight, or about 100 gm. a day, during lactation.

Effects of Maternal Protein Deficiency

Conception rate. Before the effects of low protein intake and generally deficient diet on the pregnant woman and the fetus are considered, it should be pointed out that severe dietary deficiency leads to amenorrhea and inability to conceive. This is a well established result of gross underfeeding in animals and one that must be considered in all animal experimentation. It has been found to have occurred in a number of areas where human starvation was in progress. According to Smith,[18] whose interesting observations are further considered below, the conception rate in Holland during the hunger winter of 1944–1945 fell to 30 per cent of normal. How much of this was due to absence of husbands and how much to malnutrition cannot be determined, but the latter was clearly a major factor. Sixty per cent of the women of menstrual age in the large cities of Holland developed amenorrhea, and there was a correspondingly sharp fall in the birth rate. Antonov[19] also reported a marked fall in the birth rate in Leningrad during the siege. Sydenham[20] recently reported the occurrence of amenorrhea among British civilian internees in the Stanley Camp at Hong Kong, China. During the months in which the diet was low in protein but adequate in calories, many women remained amenorrheic without losing weight. The incidence of amenorrhea fell sharply after supplies of tinned meat became available through Red Cross shipments. Sydenham concluded that although emotional shock or change of environment may have explained many of the irregularities of menstruation and the early cases of amenorrhea of short duration, the 53.7 per cent of patients with amenorrhea lasting more than three months — in some cases lasting a year or more — could hardly be explained on this basis. Malnutrition, especially deficiency of protein, appeared to be the most probable cause.

Complications of pregnancy. Williams[10] has recently reviewed the relation between protein nutrition and the course of pregnancy. He refers to the customary evidence of protein deficiency, such as depletion of body tissues, lowered serum protein, nutritional edema and lowered resistance to infections. Although these manifestations of protein deficiency occur more frequently under the stress of pregnancy, they are not peculiar to this state and are therefore not considered here. Williams considered at greater length the possible relations between protein nutrition and toxemia, the anemias of pregnancy, poor uterine muscle tone and lowered resistance to special infections during the puerperium. These may be regarded as the more particular problems of protein malnutrition affecting the health of the woman during pregnancy.

Since the cause of toxemia of pregnancy is still obscure, one who is not an obstetrician hesitates to discuss this complicated subject. Recent studies of Smith and Smith[21] point to a true toxin resulting from damage to the uterine tissue associated with abnormal estrin-progestin metabolism. Nevertheless, it may be accepted that the ultimate cause of this complication of pregnancy remains to be established, and it seems clear from several recent studies that protein metabolism is a factor of possible significance. Unquestionably, many influences are concerned, but this review restricts attention to the evidence regarding the relation of dietary protein to the incidence of toxemia.

A number of workers[11, 22–27] have presented evidence that the incidence of toxemia is far higher among women whose intakes of protein are markedly deficient or whose diets are generally poor than among those whose diets are generally good or are well supplied with protein. The difficulties involved in human studies in proving whether or not a given nutrient is responsible for a given effect are apparent to those who have attempted to investigate these relations further. Strauss[22] has contended that the most plausible assumption is that in the presence of protein insufficiency the colloid osmotic pressure of the serum protein is altered. This causes edema and a consequent disturbance in the electrolyte balance that, in turn, results in elevation of the blood pressure and other symptoms of toxemia. In such circumstances, protein may serve as a protec-

tive or therapeutic agent by virtue of its chemical and physiologic properties, rather than as a source of building materials for new tissues, as in most of the situations being considered.

Studies of pregnancies in 216 cases have been reported by Burke and her associates[27] at the Harvard School of Public Health. The patients were followed at the Boston Lying-in Hospital, with detailed dietary histories each trimester, and the diets were graded into five categories from "very poor" to "excellent." There were 28 cases of toxemia in the series. The incidence of this condition was 44 per cent among the patients whose general diets were rated "poor" to "very poor" and 8 per cent among those rated "fair," whereas among those rated "good" or "excellent" not a single case developed. This association between generally poor diet and high incidence of toxemia is impressive and has statistical significance, but when analyzed on the basis of protein alone the relation was not statistically important, although in the same direction. The number of cases is too few to justify conclusions, and further study is required. Arnell[11] found a higher incidence of toxemia among patients with a low-protein diet than among those with a liberal protein diet. Holmes[28] reported that the incidence in groups of 350 primiparous and 350 multiparous women taking low-protein diets was twice as great as that in similar groups taking high-protein diets. On the other hand, Dieckmann[28] could not confirm this relation and has expressed the view that toxemia and a low-protein intake are not related.

Reports from certain areas in which true starvation occurred during World War II, as well as during World War I, have indicated that the incidence of toxemia fell sharply among pregnant women during the periods of extreme food restriction. In studies of pregnancies and their outcome at the midwifery school of Rotterdam, Holland, before, during and following the acute famine of 1945, Smith[18] obtained rather surprising figures regarding the incidence of toxemia. During the months of acute hunger the incidence fell to about half that occurring in the same institution during the pre-hunger and post-hunger periods. The diets of pregnant women from January to April, 1945, of the so-called "hunger winter" provided according to the ration figures approximately 750 to 900 calories and 35 to 40 gm. of protein. Although there is no way of knowing how much additional food these women may have had, it is safe to assume that even at best the diets during this period were low in both calories and protein, as well as in minerals and vitamins.

The studies of the results of war shortages on toxemia are in such sharp contrast to those of other maternal dietary studies that one must examine the data carefully for an explanation of the differences. In Holland the hunger period was one of brief duration, rarely affecting more than half of any pregnancy, and the pre-hunger period provided relatively good nutritional circumstances. The more detailed dietary studies in the United States, in contrast, indicate that the women with poor diets for the most part had habitually consumed such diets before and during pregnancy. In Holland the hunger diet was one of low calories and roughly parallel reduction in protein and other essential nutrients, whereas in this country the poor diets were usually poorly balanced providing more or less adequate, sometimes excessive, calories drawn largely from classes of foods that carried little protein and other structural and regulatory essentials. A factor that may have influenced the results in Holland was the sharp fall in the conception rate. It could well be that the women in Holland who were chronically undernourished, and hence presumably predisposed to the development of toxemia, became amenorrheic in a relatively short time on such an inadequate diet and hence did not conceive. The potentially toxemic women may thus have been removed temporarily from the population of the maternity hospital.

Although there is still controversy among well informed persons concerning the cause of toxemia, it is generally accepted that a high-protein diet does not predispose the patient to the condition. Furthermore, the major weight of evidence appears to be that toxemia occurs oftener among chronically malnourished than among well nourished women, protein being one of the nutritional factors frequently lacking. Most workers, including those in my group and others who have obtained similar results, are agreed that although definite conclusions cannot yet be drawn the subject is an important one for further investigations.

Anemias of pregnancy. A physiologic reduction in the number of red cells and in the hemoglobin takes place normally in midpregnancy and is apparently a dilution phenomenon. The hypochromic anemia often seen in late pregnancy is generally considered to be an exaggeration or prolongation of this physiologic change. Bethell,[29] reporting a 25.4 per cent incidence of anemia in a group of 484 pregnant women in Michigan, found a relation between deficiency of dietary iron and hypochromic anemia. This type of anemia often responds poorly to iron therapy alone and has been reported to respond much more satisfactorily to a combination of a diet high in animal protein and medicinal iron.

True macrocytic anemia of pregnancy is rarely encountered in this country. Bethell, in the study mentioned above, found a relation between macrocytic anemia and an inadequate intake of protein. Severe macrocytic anemia of pregnancy is reported to be frequent in India. This type of anemia carries with it high maternal and high fetal mortality rates. Napier and Neal-Edwards,[30] who have studied the condition extensively in India, point out that its incidence is highly correlated with a low economic status and with diets low in protein of animal origin.

They believe that it is probably dependent on a lack of complete proteins but possibly also on a deficiency of one or more of the factors in the vitamin B complex. This type of anemia usually responds to an increased intake of animal protein and of the factors of the vitamin B complex.

Labor and delivery. There is little evidence that protein deficiency in the mother contributes directly to prolonged or difficult labor and to other complications at or following delivery. Poor development of the uterus was found by Wallace[31] to be a striking end result of low protein, low-calorie diets in sheep. Uterine inertia and prolonged labor have often been considered attributable in individual cases to poor nutritional state. In the studies at the Boston Lying-in Hospital the average length of labor of the primiparous women was the same in the group with poor diets as in that with good diets.[27] It is of interest, however, that in this series of 216 cases there were many more difficult types of delivery in the patients with poor to very poor diets than in those with good or excellent ones, despite the fact that the infants in the former group were on the average 3 pounds lighter in weight. It is generally recognized that large babies make for more difficult deliveries than small ones do. Hence, other things being equal, the mothers with poor diets should have had shorter labors and easier deliveries. The assumption may therefore be made that the women in the poor-diet group were not otherwise so fit for labor.

Frequency of abortions and stillbirths. Arnell,[11] in the studies referred to above, showed that when the maternal dietary protein was 85 gm. or more there was no fetal mortality and that when it was between 70 and 85 gm. daily the mortality was only 2.2 per cent. On the other hand, when the protein consumed was between 42.5 and 54 gm., the fetal mortality rose to 5.5 per cent. In another report of the 216 cases referred to above,[32] there were no abortions probably because enrollment was not until the end of the third month or later. There were, however, 5 stillbirths, all of which occurred in pregnancies of women with very poor diets. All the women whose babies were stillborn consumed diets that were inadequate in protein, and in all but 1 case the calories were rated inadequate. Two of the 3 neonatal deaths in this series also occurred in the group with poor to very poor maternal diets. Ebbs[24] found that of the 14 infants lost in a total of 310 pregnancies, all were in the group with poor maternal diets. There were 7 miscarriages, 4 stillbirths and 3 neonatal deaths in his series. Williams,[12] however, found no relation between maternal diet and the condition of the infant at birth.

Smith's[18] data from Holland are inconclusive on these points as are the figures of Antonov,[19] which cover the period of the siege in Leningrad. It is impossible to draw conclusions from changes in rates representing proportions of live births, when the birth rates were changing as rapidly as they were in Holland and Leningrad at the times of these studies.

Premature births. In our studies in Boston all prematurely born babies — that is, infants weighing less than 2.25 kg. (5 pounds) at birth — were born to mothers whose diets were in the lowest general rating. Here again, the work of Ebbs,[24] the Peoples League of Health[25] and Balfour,[26] showed the same trend, but that of Williams[12] failed to do so. Smith[18] also found a slight but not statistically significant increase in the percentage of births of infants weighing under 2.25 kg. during the hunger period in Holland. Antonov[19] observed that the rate in Leningrad was 41.2 per cent of the total births during the siege but fell to 6.5 per cent in the first six months after it had ended. The marked reduction in the birth rates during these periods complicates the interpretation of these figures as they do those for abortions and stillbirths.

TABLE 1. *Relation of Birth Weight and Length to Total Protein in Maternal Diet during Last Six Months of Pregnancy (according to Burke et al.[8]).*

Average Total Protein	Birth Weight*		Birth Length	
	Male Infants	Female Infants	Male Infants	Female Infants
gm.	*lb.* *oz.*	*lb.* *oz.*	*cm.*	*cm.*
Less than 45	6 8	5 14	47.6	46.8
45–54	7 0	6 14	49.3	48.7
55–64	7 7	7 8	50.2	49.9
65–74	8 0	7 12	51.4	50.3
75–84	8 5	8 1	52.0	51.4
85 and over	9 2	8 8	53.3	52.4

*No infants weighing under 5 pounds included.

The evidence suggests that inadequate protein during pregnancy, especially when enhanced by inadequate calories, increases the chances of premature onset of labor. Again, it must be concluded that although poor maternal diets and a high incidence of abortions, stillbirths, premature births and neonatal deaths are frequently associated, the nature of this relation is not yet known.

Size and development of the infant at birth. The evidence regarding the association between maternal diet and the size and development of the infant at birth is much stronger and more convincing than that for the relations thus far considered. It is difficult to separate exactly the infants who are small and poorly developed at birth because of premature onset of labor and those who have reached full term showing evidences of retarded fetal growth and development. The former is primarily a maternal effect, and the latter a fetal one. For this purpose premature birth is usually determined arbitrarily on the basis of a selected birth weight, and in our studies a weight of 5 pounds has been used. Table 1 presents birth weights and birth lengths according to the quantity of protein in the maternal diet during pregnancy.

The progressive increase in average birth length and birth weight with increasing amounts of dietary protein during the latter part of pregnancy is striking.

Smith,[33] in his study of birth weights and birth lengths in Holland, found a sharp drop during the hunger winter and an almost equally abrupt rise as Holland emerged from the period of severe malnutrition. This association between the size of the newborn and the adequacy of rations may well have depended on the protein content of the maternal diet as well as on the caloric content, since the Dutch diets were known to be low in protein during this period and since low calories make the diet even less satisfactory in protein. In studies of babies born in Leningrad during the siege, Antonov[19] showed similar trends in birth weights, the average during the first half of 1942 being approximately 0.5 kg. lower than that for the corresponding period of 1941 before the siege. During the second half of 1942 (after the siege), the average weight had risen about half the amount lost.

Wallace[31] has shown that when the diets of sheep are made low in calories and protein in the last half of pregnancy the weight and length of the newborn are markedly lowered. Using the same mother animal Wallace reversed the results by increasing these components of the dietary intake of the pregnant animal. Whereas it is not possible to say from these experiments that protein was the only factor responsible for the differences in the rates of growth of the fetuses, it is possible to conclude that the combined intake of calories and protein in the latter part of pregnancy was the primary variable.

The relations found by my associates in Boston, the evidence of Smith from Holland, the work of Antonov in Leningrad and recent English studies reviewed by Garry and Wood[16] provide strong evidence that if the diet is low in protein during the latter part of pregnancy, there is a tendency for the infant to be born prematurely or to be relatively immature at birth.

Evidence of retarded osseous development in infants born to mothers whose diets were poorly provided with protein has been presented.[34] Osseous ratings of "advanced," "average" and "retarded" were given on the basis of the presence or absence of certain osseous centers at birth in roentgenograms of the knee, hand and foot. When the maternal diet was excellent in protein, 57 per cent of infants were advanced in osseous development, and 14 per cent retarded, whereas when the maternal diet was very poor in protein no infants were advanced and 71 per cent were retarded. Although this relation appears to be significant, it must be remembered that certain other nutrients closely associated with protein in food may have been involved. It is known, however, that protein forms the matrix for bone growth, and there are other reasons for believing that protein may be the principal factor. Wallace[31] has presented data on sheep that tend to confirm this relation. He found much poorer skeletal formation in the young of the sheep inadequately fed in protein and calories in the latter part of pregnancy than in those well fed during this period.

The studies of Wallace referred to above showed that changes occurred in the maternal stores of protein in conjunction with changes in the diets. His results indicate that the fetus is parasitic on the mother only to a degree and that when her protein stores are depleted to any major degree she appears to retain the remaining stores as if some protective mechanism were operative. These studies also show that when the maternal animals are starved in relation to calories and protein in the latter part of pregnancy the livers of the young are small, the increase in size during the last half of pregnancy being approximately 8 per cent of normal.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33141

PRESENTATION OF CASE

First admission. A nineteen-year-old unmarried girl was admitted to the hospital because of pain in the lower back.

For three years the patient had suffered from pain over the coccygeal region. The pain was nonradiating and was aggravated by long sitting or standing, but was not noticeably increased by rising or sitting down. She had noticed some tenderness and pressure over that area. A year prior to admission a pilonidal sinus had been removed from the area, without relief from pain. She suffered a great deal from riding in an automobile and sitting in a soft seat, and the pain was often worse at night.

No contributory past history was obtained.

On physical examination the only positive finding was pain on pressure over the coccygeal region and just to the right of the scar from the operation for pilonidal sinus. Examinations of the blood and urine were negative, except for a white-cell count of 12,700. The differential count was normal. A blood Hinton test was negative. X-ray films taken in the Out Patient Department before admission revealed the coccyx to be poorly visualized and somewhat fragmented. There was a faint suggestion of a soft-tissue mass, measuring 5 cm., in the midline, at the extreme distal tip of the coccyx.

X-ray examination on admission revealed that the lower segments of the coccyx were absent. The previous films were not available for comparison.

While in the hospital the patient noted a small amount of mucus in the stool and stated that she had noticed this once or twice about two or three months previously. She denied any pain during bowel movements. There had never been any blood in the stools, although the mucus had once been slightly pink. After sigmoidoscopic examination the pain disappeared completely, and the patient was surprised at her ability to lie in any position. Three days later the pain was still only mild. A psychiatrist discovered considerable emotional problems relating to the family. He thought that the patient was somewhat emotionally immature. The mother was domineering, and there was competition with a brother for parental affection. Study on the psychiatric service was recommended. The patient was discharged with instructions in gluteal exercises and sitting.

Final admission (five months later). The patient was followed in the Psychiatric Out Patient Clinic without improvement. Five months later she was noted to have erythema and induration in the region of the scar, possibly as a result of excessive physical therapy. She was noted to be stooping somewhat and was again admitted to the hospital. She localized the pain largely to the tip of the sacrum. No mass was felt by several examiners. Examinations of the blood and urine were negative. An x-ray film revealed that the coccyx and lower segment of the sacrum were missing and there was a soft-tissue mass, measuring 7 by 4 cm., within which there were areas of calcification or bone remnants. The edge of the remaining segment was somewhat ragged. Subsequent to this report an extremely hard, tender mass was palpable by rectum or pelvic examination corresponding to the x-ray finding at the lower end of the sacrum. An x-ray film of the chest was negative. The blood calcium was 8.9 mg., and the phosphorus 3.3 mg. per 100 cc., and the phosphatase 15.7 Bodansky units.

About a month after admission an operation was performed.

Differential Diagnosis

Dr. Channing C. Simmons: In all these cases of bone lesions three main conditions should be borne in mind: skeletal disease, an inflammatory condition and tumor, either primary or metastatic. Keeping these possibilities in mind, let us analyze this case. The patient was highly nervous, and complained of pain in the region of the coccyx. She had been operated on five months previously for pilonidal sinus. The pain was relieved by sigmoidoscopy. The x-ray films showed some trouble with the coccyx. Reading between the lines I believe that, at that time, a diagnosis was probably made of a low-grade infection, such as osteomyelitis, secondary to the pilonidal sinus. Why the pain was relieved by sigmoidoscopy, I do not know; that is not the ordinary treatment for either osteomyelitis or coccygalgia. I also do not know why nothing more was done after the findings showed a definite lesion of the coccyx.

May we see the first x-ray films?

Dr. Toufic H. Kalil: This is the soft-tissue mass referred to, and in the lateral view it can be seen extending down to replace the coccyx. The ragged appearance of the bone denotes destruction.

Dr. Simmons: The patient was readmitted with a definite mass in that situation, and the pain continued. In this second series of films the mass appears larger than it was previously.

The one positive finding other than tumor is the high phosphatase in the blood. From the description of the x-ray examination there was bone destruction with new bone formation in the tumor, and the high phosphatase was probably due to new bone formation. We can rule out disease of the liver and kidney, in which the phosphatase may be high. The temperature was normal; the urine was normal. There is no evidence, so far as I can see, although we have no complete skeletal x-ray films, of generalized metabolic disease.

We have a definite possibility of an inflammatory condition. The patient had a pilonidal sinus, which is notoriously difficult to cure by operation, and there may have been a low-grade secondary infection persisting with involvement of the bone. Tuberculosis, I should think, can be ruled out. I have not seen anything suggesting that in the record or past history. The blood Hinton test was negative; that test, however, is sometimes negative with bone syphilis.

We then come down to some form of tumor, primary or metastatic. One primary tumor that does occur in this region is chordoma, which is frequently seen in the sacrum, although it may arise at the base of the skull, or any point in the spinal column. One should think of chondroma, Ewing sarcoma and ordinary osteogenic sarcoma, the last being relatively rare in this situation, however.

Metastatic tumors may have occurred from the rectum or cancer in any part of the body, although the patient was only nineteen, which is young for a primary carcinoma with metastases. This is not conclusive, however, because cancer does occur in the young. The only positive finding suggesting cancer is the mucus passed by rectum.

I do not see how one can rule out Ewing sarcoma.

I cannot make a diagnosis in this case. On the facts presented the most probable diagnosis is a chordoma, which is the most frequent tumor in this situation. I am probably wrong because this diagnosis seems so obvious and we know that all the cases that Dr. Mallory puts up to us are problems. A chondroma is a second possibility, and the third is malignant lymphoma of some sort. I think that it is impossible to make a definite diagnosis without a biopsy.

Clinical Diagnosis

Tumor of sacrum and coccyx, unspecified.

Dr. Simmons's Diagnosis

Chordoma?

Anatomical Diagnosis

Benign giant-cell tumor of coccyx and sacrum.

Pathological Discussion

Dr. Tracy B. Mallory: The opinion on the ward was the same as Dr. Simmons's: that it was impossible to make a diagnosis without a biopsy. The patient was operated on, and a segment of the tumor removed. I believe that while we were attempting to make a frozen section, the surgeon went ahead with the resection of the lower portion of the sacrum and the coccyx. The tumor proved rather puzzling on frozen section, as such lesions often do. It consisted of a considerable amount of fibrous tissue in which there were spicules of osteoid and a large number of foreign-body giant cells. On the basis of the general appearance I thought that benign giant-cell tumor was the most probable diagnosis. When the better sections came through, we were in somewhat the same predicament as Dr. Simmons. The picture varied from one area to another; the tumor was much more fibrous and had a good deal more bone formation than is usual with a benign giant-cell tumor. The picture in some places suggested a condition that we call fibrous dysplasia of bone. In other areas large foreign-body giant cells were numerous. We made a final diagnosis of benign giant-cell tumor, although the possibility that it should be classed as fibrous dysplasia still exists. I can remember one other case of benign giant-cell tumor of the spinal column that extended out into the soft parts and eventually spontaneously broke through the skin of the back. The diagnosis was made by biopsy, and following x-ray therapy the lesion disappeared almost miraculously fast, and

the patient has had no subsequent difficulty. Although this is a rare location for a benign giant-cell tumor, it is a possible one.

Dr. Simmons, have you anything further to say?

Dr. Simmons: In any of these cases in which the radiologists and clinicians are at a loss regarding the diagnosis, when the pathologist gets the section he may be puzzled too.

CASE 33142

Presentation of Case

A forty-seven-year-old housewife entered the hospital because of a mass in the right axilla.

Three years before admission pain and weakness had developed in the right shoulder and axilla. A mass was discovered. The pain disappeared after a course of x-ray treatment. A year and a half later a second course of x-ray therapy was given because of the reappearance of pain. A few weeks before admission the mass was again present and somewhat painful. Three and two weeks prior to admission single doses of x-ray therapy were directed at the axilla. There was doubt whether irradiation altered the size of the mass.

No masses had ever been felt in the breasts, nor had there been pains in other parts of the body. No lymph-node enlargement had ever been noted. The system review and past history were noncontributory.

Physical examination showed a large, obese woman who weighed about 220 pounds and appeared in good health. In the right axilla there was a mass measuring 8 by 8 cm. that moved with the scapula. It felt firm but not stony hard, and was smooth and slightly tender. The overlying skin was not adherent, nor was the mass adherent to the chest wall. No lymphadenopathy was present.

The temperature, pulse and respirations were normal. The blood pressure was 190 systolic, 110 diastolic.

Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 6200, with 53 per cent neutrophils. The urine gave a + test for albumin, and the sediment contained 25 red cells and 15 white cells per high-power field. The blood calcium was 8.9 mg., the phosphorus 2.2 mg., and the total protein 7.3 gm. per 100 cc., and the phosphatase 3.0 Bodansky units. On x-ray examination the heart and lungs appeared normal. There was evidence of an old healed fracture of the distal third of the right clavicle. There was an oval soft-tissue mass in the medial wall of the right axilla, measuring approximately 11 by 6 cm. The outer wall was fairly well demarcated and smooth in outline. The upper two thirds of the lateral border of the scapula was irregular in outline.

An operation was performed on the eighth day.

Differential Diagnosis

Dr. Grantley W. Taylor: The history is deplorably silent about whether the tumor disappeared after x-ray treatment. Perhaps we should see the x-ray films.

Dr. Toufic H. Kalil: The soft-tissue mass is best seen on this film. It measures 11 by 6 cm. and has a smooth, well defined outer border. The involved portion of the scapula is demonstrated by the irregular lateral margin produced by a small amount of bone destruction.

Dr. Taylor: In a discussion of the diagnosis of these lesions involving bone in the preceding case Dr. Simmons referred to the possibility of confusing inflammatory conditions and metabolic disturbances with bone tumors. It seems to me that we have nothing to suggest an inflammatory process or any generalized metabolic disturbance in this case. We are dealing with an axillary tumor, and there is little to go on except the tumor itself, the x-ray findings and the fact that the patient was apparently well in spite of the presence of tumor for over three years.

Was this a tumor of bone with soft-part extension, or tumor of the soft parts with erosion or irregularity of bone because of the propinquity of the process to the bone? I do not believe that one can say definitely. Dr. Kalil might like to make a statement regarding whether that amount of bone distortion could be due to impingement of a tumor on the soft parts.

Dr. Kalil: I should expect a smooth erosion rather than this type of irregularity in such a case.

Dr. Taylor: When we consider the bone tumors in this region we at once raise the question whether they are benign or malignant. In favor of a benign tumor in the case under discussion is the long course and the patient's excellent health in spite of the long course. We have one additional fact in the history that may be of some significance — namely, that x-ray treatments had been used, with adequate control of the symptomatology for some time. It would be helpful to know whether there was any change in the mass as a result of the previous irradiation. It is interesting that x-ray therapy relieves the pain in many conditions, in which it can almost be regarded as a type of physiotherapy. There seems to be something specific about the relief of pain by x-ray treatment in a large diversity of cases that are not necessarily neoplastic or malignant.

Dr. Kalil is unwilling to say that this amount of bone disease was due to the pressure of an adjacent tumor of the soft tissue. We must concentrate on bone tumors or tumors that may involve bone. Of the malignant tumors we must consider whether we are dealing with metastatic or primary tumors. This was a perfectly healthy person with nothing in the history to suggest metastases from any other part of the body. The one positive finding on laboratory examination was that the urinary sediment con-

tained 25 red cells and 15 white cells per high-power field. There was some albumin. I assume that that may not have been a catheterized specimen, because no attention seems to have been paid to it. If it had been a catheterized specimen, it seems to me that one would have to investigate further, at least to the extent of a pyelogram or some other investigation of the genitourinary tract.

Could this have been a metastasis from a primary neoplasm of the genitourinary tract? It had been present for three years. In that time the patient should have had symptoms referable to the kidneys or bladder. I therefore think that we must concentrate on the notion that this was a primary tumor. The results of x-ray treatment in the past argue a little more in behalf of a malignant than of a benign tumor, but the long course and the excellent health are more in favor of benign than malignant tumor. We can bet our money and take our choice. The fibromas, fibrosarcomas and periosteal fibrosarcomas seem to share the properties of soft parts and bone, and give rise to considerable soft-part tumors with less extensive bone involvement than occurs with osteogenic sarcoma or Ewing tumor or some of the other primary bone tumors. Chondromas and chondrosarcomas are likely to show evidence of bone formation or calcification within the tumor and to be lobular on palpation and on x-ray study of the soft-tissue swelling. We have had a certain number of synoviomas, but they are usually highly malignant, and rapidly growing. They may occur in this region not immediately in a joint but more or less removed from the joints and skeletal structure. Some of the ones we have seen here have given some indication of calcification. I do not see any evidence of calcification in this tumor.

Finally, we come to the group of lymphoblastic tumors that may involve bone and present soft-tissue tumors that respond gratifyingly to x-ray therapy. It is interesting that on physical examination no reference was made to the character of the skin in the axilla after two courses of x-ray therapy. It seems that that point might be relevant, because it would give some indication of the amount of x-ray treatment that had been given to relieve symptoms and perhaps to make the tumor disappear.

There are other rarer tumors that we can allude to simply for the sake of completeness, but I do not believe that we can make a diagnosis. We are confronted with a mass that involved the bone, and we shall have to resort to immediate pathological examination; the decision regarding the character of the tumor depends on the result of such examination. I favor a periosteal fibrosarcoma as a likely diagnosis, but it is anybody's guess.

Dr. Norman J. Wilson: I might add that this woman insisted that the tumor in her opinion had decreased with each course of x-ray therapy except the last, which had been inadequate. She had definite relief of pain. Just how much the tumor decreased we could not tell because we had only the patient's word for it. It did not disappear entirely, however, because she was always able to feel it and was conscious of its presence.

Dr. Taylor: That should help me, but it does not.

Dr. Tracy B. Mallory: Will you describe the operation, Dr. Wilson?

Dr. Wilson: We biopsied this tumor preoperatively and waited for the report before proceeding with treatment. We had considerable difficulty getting at the tumor. On the first attempt, we found a well encapsulated structure and took three good pieces of tissue from what we thought was tumor but discovered to be nothing but muscle overlying the tumor; the muscle had evidently been heaped up there as a result of reaction around the tumor and of the x-ray treatment. We were forced to make a larger incision and even then had considerable difficulty in getting a satisfactory biopsy. Dr. McKittrick resected the scapula below the spine along with the tumor en masse. At operation, when we approached the tumor we could not determine whether it was attached to the scapula anywhere, and the scapula to all intents and purposes was normal.

Clinical Diagnosis

Fibrosarcoma of axilla?

Dr. Taylor's Diagnosis

Periosteal fibrosarcoma.

Anatomical Diagnosis

Fibromyxosarcoma.

Pathological Discussion

Dr. Mallory: The biopsy that was finally taken on this patient showed a neoplasm that we described as a fibromyxoma. After the resection and further sections we qualified that slightly and decided to call it a slowly growing fibromyxosarcoma. It was on the borderline of malignancy and well circumscribed but not completely encapsulated. Since we were unable to make out any point of true attachment to the scapula or its periosteum we thought that it was a tumor of the soft parts, with secondary erosion of the scapula, which is the other possibility that Dr. Taylor mentioned.

Dr. Taylor: I should have said — and meant to say — that, having argued against neoplastic disease on the grounds that this patient was in excellent health, I finally made a diagnosis of a type of malignant process that is frequently slowly growing in its propensity to spread and does not impair the patient's general condition for a long while — namely, a periosteal fibrosarcoma.

Addendum to Case 33041.* A sixty-nine-year-old farmer, previously treated for a chondroma of the popliteal space by excisional surgery, was readmitted to the hospital two weeks after discharge. He complained of severe pain and stiffness in the right knee that had steadily increased since operation.

To determine whether the pain and limitation of motion were bona fide and to estimate the range of motion of the knee joint when the factor of pain was eliminated, a manipulation was done under Pentothal anesthesia. The range of motion of the knee was from 90 to 170° — with an average of 80° — and was all that could be obtained without force.

After the manipulation, the patient complained that the knee was more painful than ever, and he held the knee at 150° and resisted motion in both directions. The x-ray films at that time showed a recurrence of the tumor. There were multiple areas of calcification in the posterior aspect of the joint. The patient became anxious and worried about "cancer" when he was advised that only amputation would relieve the pain and cure the tumor. He was sent home to think the matter over more thoroughly and to calm his fears.

He returned to the hospital for a third admission, eight weeks after the previous operation. He asked that the leg be amputated because the pain was even severer than previously and there was no motion in the knee joint, which he held at 115°. He objected to any attempt at passive motion. There was palpable induration of the joint capsule. The entire knee was acutely painful to palpation, especially over the joint line on both the medial and the lateral aspects.

Under nitrous oxide, oxygen and ether anesthesia, a midthigh amputation was done nine weeks after the previous operation in which the original tumor had been removed from the popliteal space. Pathological study of the specimen showed a complete knee amputation sharply 10 cm. above the joint and 16 cm. below, with overlying muscle, soft tissues and skin. Posterior to the knee joint there was a firm cartilaginous, somewhat nodular, tumor mass measuring 6.5 by 5 cm. and extending posteriorly for 3 cm. Although the mass was firmly adherent to the head of the tibia, no direct connection of the growth was found, and it was likewise separated a few millimeters from the femoral head. The synovial wall was involved; a few small seedings were noted on the articular surface of the tibia and in the anterior synovial membrane, and even over the tip of the patella there was a 4-mm. seed (Fig. 1). The popliteal artery and vein were free of involvement. Section through the tumor proper revealed a fairly homogeneous cartilage, with a few small, soft, brown areas and foci of hemorrhage. The surface of the

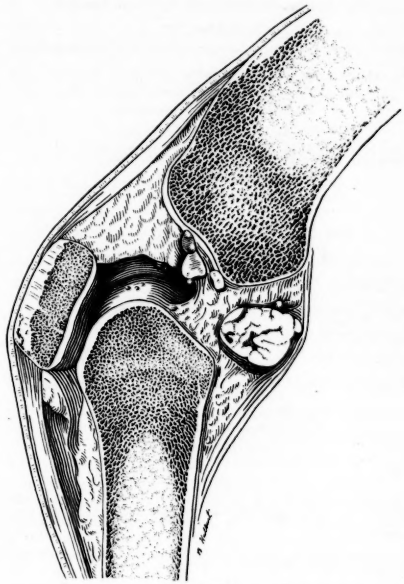

FIGURE 1.

tumor was smooth but without a definite capsule. There was a small amount of red marrow on the head of the tibia, but otherwise it was fatty.

The tumor was composed of many large and small separate islands of well differentiated cartilage, with few cells and abundant hyaline matrix. Nearly all the islands were surrounded by narrow borders of myxomatous tissue that in places showed suggestive patterns of transition into cartilage. It was not possible to be certain whether this myxomatous tissue represented part of the neoplasm or a metaplastic process in the surrounding synovia. Although the usual histologic features of cancer were largely lacking, the infiltrative character and the rapid recurrence justified a diagnosis of chondrosarcoma.

The patient was discharged with an artificial limb. The stump was painless and functioned well.

MARSHALL R. URIST, M.D.

*Case Records of the Massachusetts General Hospital (Case 33041). *New Eng. J. Med.* 236:145-148, 1947.

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PUBLIC-HEALTH SERVICES IN MASSACHUSETTS

The shortage in trained professional workers has created a critical situation in the Massachusetts Department of Public Health and Department of Mental Health and in many municipal health departments in the Commonwealth. At the present time these departments are operating under the handicap of a greatly reduced personnel, including physicians, nurses and other workers. For instance, in the Department of Public Health about 50 per cent of the positions filled by physicians and 40 per cent of those occupied by hospital workers are now vacant. Unless remedial steps are soon taken, the vital health services of these departments will be seriously impaired.

The shortage of physicians has been brought about, to a large extent, by the existing low-salary levels. The present scale of salaries of physicians in the service of the Commonwealth is considerably below those of the federal government and of many states. In fact, Massachusetts ranks thirty-eighth among the states in the average salary levels of public-health physicians. As a result there has been a continuous loss of capable men, attracted elsewhere by more lucrative positions in the federal and state services or in general practice, and a corresponding inability to fill these vacancies with well trained men, since inadequate salaries preclude competition with other agencies.

At its February meeting, the Council of the Massachusetts Medical Society, recognizing the gravity of the situation, voted to instruct the Committee on Legislation to give its support to an active program for raising the salary levels of physicians and other professional workers in the services of the Commonwealth or one of its political subdivisions. The Society considers that the scale of salaries in these state and local departments should be placed at levels that will allow Massachusetts to compete with outside agencies for the services of properly trained persons. In brief, the establishment of salaries on a competitive level appears to be the most logical and practical step for correcting the present unfortunate situation.

" . . . TO GROW IN WISDOM"

The part that the doctor should play in marriage counseling and in sex instruction was the subject of a talk given recently before the Planned Parenthood League of Massachusetts by Dr. James C. Janney, president of the Marriage Study Association. Dr. Janney's belief that many marriages are wrecked because of a lack of understanding and of good judgment in sex matters will be accepted by anyone who has given the subject any thought, and it must be equally apparent that the physician should be the one best equipped to give advice on the subject.

How the physician should acquire such knowledge, however, and how he can be interested in accepting what is clearly a professional obligation are difficult questions to answer directly. Dr. Janney

suggests that medical students should receive training in sex relations, on the basis of the average physician's inadequate equipment in this field, and undoubtedly he is right. At least the student would be made to realize the importance of the subject, and that it is in his province if he really wishes to make of himself the wise counselor that he should be. One difficulty, however, is that scientific knowledge is increasing by leaps and bounds, that the medical curriculum is already overloaded and that each department chronically needs more time in which to deliver its fundamental message.

Perhaps the curriculum of the average school is not now well planned; undoubtedly there is too much obstetrics for the future ophthalmologist, too much orthopedics for the embryonic laryngologist, too much surgery for the potential psychiatrist. The medical school, after all, can turn out only a doctor of medicine, not a physician or a surgeon, a dermatologist, an allergist or a pediatrician. The duty of the school, as it sees itself, is to impart basic principles and to give the student at least a speaking acquaintance with the various specialties of medicine and surgery. The medical school does not so much take the student onto a high place and point out the promised lands spread before him as it takes him into a broad valley from which he can see the peaks that challenge him to climb. The graduate himself, by his own efforts, having seen the range spread out in panorama before him, must essay the trail that will take him to his chosen peak.

Dr. Oliver Wendell Holmes, just seventy-five years ago last March, delivered a valedictory address to the graduating class of Bellevue Hospital College. His title was "The Young Practitioner," and his thesis, the theory — not altogether new — that the young graduate, bursting with knowledge, was not really a physician until he had gone through a depleting process to get rid of his extra medical-school learning and had replaced it with the fruits of experience. "Hard work," counseled the Autocrat, "will train it off, as sharp exercise trains off the fat of a prize-fighter." And again, from the same source, "Knowledge that is not wanted dies out like the eyes of the fishes of the Mammoth Cave."

Some knowledge of sex-counseling should undoubtedly be imparted to each candidate for the medical degree, even for his own sake, just as he is required to have at least a smattering of ignorance on the mechanics of the birth of twins. Nothing, however, will make the student a good physician in this or in other matters unless he wishes to transmute his information into the right type of wisdom. "If you ship a poor cask of wine to India and back," said Dr. Holmes in 1871, "if you keep it half a century, it only grows thinner and sharper."

NEW ENGLAND DIABETES ASSOCIATION

Although insulin has been in use for over twenty-five years, the number of deaths attributed to diabetes continues to increase, and the disease ranks eighth among the leading causes of death in the United States. The New England Diabetes Association, a notice of whose organization meeting on April 16 appears elsewhere in this issue of the *Journal*, is an outgrowth of occasional, informal gatherings held, for several years before the outbreak of World War II, by a group of physicians interested in the growing problem of diabetes as a disease affecting a sufficient proportion of the population to be considered a matter of concern to the community at large.

The purpose of the new association is to afford physicians, dietitians, nurses and other scientific workers especially interested in the welfare of diabetic patients an opportunity to meet regularly for discussion of the manifold problems of the diabetic patients in New England, conservatively estimated to number 80,000. Similar organizations have been of great value in the treatment of heart disease, tuberculosis, cancer and the arthritides. The formation of the New England Diabetes Association occurs at a time when the United States Public Health Service, with which it has no direct connection, is displaying an active interest in diabetes as a public-health matter. Physicians generally and specialists in diabetes in particular will welcome the efforts of the new organization.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

DOLE — Mary P. Dole, M.D., of Shelburne, died February 23. She was in her eighty-fifth year.

Dr. Dole received her degree from Woman's Medical College of Baltimore in 1888.

Several nieces and nephews survive.

GIGGER — Augustus G. Gigger, M.D., of Falmouth, died November 27. He was in his sixty-ninth year.

Dr. Gigger received his degree from Boston University School of Medicine in 1906.

JENNINGS — John G. Jennings, M.D., of Weston, died February 17. He was in his fifty-ninth year.

Dr. Jennings received his degree from Tufts College Medical School in 1915. He was a member of the staff of the Massachusetts Eye and Ear Infirmary and of the Waltham Hospital, as well as a member of the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow, a daughter and a son survive.

KEES — Philip A. Kees, M.D., of West Springfield, died November 4. He was in his thirty-ninth year.

Dr. Kees received his degree from University of Minnesota Medical School in 1936. He served as a medical officer in World War II, receiving the Purple Heart, The Bronze Star for valor and the Silver Star for gallantry in action. He was a fellow of the American Medical Association.

His widow and three children survive.

SEDGLEY — Frank R. Sedgley, M.D., of Redwood City, California, died February 12. He was in his sixty-eighth year.

Dr. Sedgley received his degree from Boston University School of Medicine in 1902. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow survives.

SMITH — Roswell H. Smith, M.D., of Edgartown, died February 12. He was in his fifty-third year.

Dr. Smith received his degree from Middlesex University School of Medicine in 1922.

His widow and two daughters survive.

TYNAN — Joseph P. Tynan, M.D., of South Boston, died recently. He was in his sixty-third year.

Dr. Tynan received his degree from Tufts College Medical School in 1910.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SHORTAGE OF CONTAINERS FOR BIOLOGIC PRODUCTS

The shortage of containers for serum, vaccines and blood products is at present more critical than ever, and deliveries of new supplies cannot be expected in less than five or six months. A further complication arises from the great increase in the demand for biologic products. During the past six months distribution of certain products has increased, as against one year ago, to the following extent: diphtheria antitoxin, 94 per cent; diphtheria toxoid, 160 per cent; Schick outfits, 159 per cent; typhoid vaccine, 47 per cent; and immune serum globulin, 303 per cent. Distribution of plasma begun in March, 1946, has totaled 16,748 units, and 4458 pints of whole blood have been issued since May, 1946, when this service was begun.

The Department of Public Health cannot maintain the present rate of distribution unless empty containers or unused products of all types are returned. Blood bottles in particular represent a considerable expense to the Commonwealth, and their prompt return is essential if this service is to be continued. Physicians, hospitals and health agencies are most urgently asked to co-operate with the Department in the present emergency, as they did so outstandingly during the war, by returning as many containers as possible, either to local board-of-health depots, to district health offices or directly to the Division of Biologic Laboratories. When other transportation cannot be arranged, large shipments may be sent express collect to the Division of Biologic Laboratories, 375 South Street, Jamaica Plain. For detailed arrangements or information telephone ARNold 4127.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1947

Résumé

Diseases	January 1947	January 1946	Seven-Year Median
Chancroid	1	3	3*
Chicken pox	2,391	1,023	1,798
Diphtheria	77	10	14
Dog bite	522	487	511
Dysentery, bacillary	10	4	6
German measles	108	73	130
Gonorrhea	360	663	357
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	1	1*
Malaria	7	52	1
Measles	1,885	1,018	1,018
Meningitis, meningococcal	9	24	18
Meningitis, Pfeiffer-bacillus	3	3	3
Meningitis, pneumococcal	1	7	7†
Meningitis, staphyloccal	0	0	0†
Meningitis, streptococcal	0	1	0†
Meningitis, other forms	1	3	2†
Meningitis, undetermined	4	4	5†
Mumps	666	698	913
Pneumonia, lobar	142	325	390
Poliomyelitis	5	0	2
Salmonellosis	13	5	5
Scarlet fever	659	804	1,200
Syphilis	311	617	417
Tuberculosis, pulmonary	277	249	213
Tuberculosis, other forms	15	5	17
Typhoid fever	3	0	2
Undulant fever	3	1	2
Whooping cough	895	480	625

*Three-year median.

†Five-year median.

Comment

Interest in communicable diseases continues to focus on the increased prevalence of diphtheria. The number of cases reported in January is nearly eight times the number in the same month in 1946, and more than five times the seven-year median. Boston and New Bedford, which have had an increased prevalence during the last three years, continued to report the bulk of the cases. The disease appears, however, to be spreading into the Connecticut Valley, and an upward trend can be expected in that area unless immunization procedures are redoubled.

Other diseases above the seven-year median for the month were chicken pox, bacillary dysentery, measles, poliomyelitis, salmonellosis, pulmonary tuberculosis and whooping cough.

Among the diseases below the seven-year median were meningococcal meningitis, mumps, lobar pneumonia and scarlet fever.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston, 30; Brookline, 1; Cambridge, 1; Chelsea, 8; Clinton, 1; Everett, 2; Fall River, 1; Greenfield, 2; Holyoke, 1; Ipswich, 1; Lowell, 3; Lynn, 2; New Bedford, 12; Palmer, 2; Randolph, 1; Somerville, 4; Springfield, 2; Stoughton, 1; Wayland, 1; West Bridgewater, 1; total, 77.

Dysentery, amebic, was reported from: Boston, 1; total, 1.

Dysentery, bacillary, was reported from: Salem, 1; Worcester, 5; Wrentham, 4; total, 10.

Malaria was reported from: Boston, 2; Cambridge, 1; Springfield, 1; Taunton, 1; Williamstown, 1; Worcester, 1; total, 7.

Meningitis, meningococcal, was reported from: Agawam, 1; Boston, 2; Framingham, 1; Greenfield, 1; Lowell, 1; Mansfield, 1; Newton, 1; Norton, 1; total, 9.

Meningitis, Pfeiffer-bacillus, was reported from: Brockton, 1; Everett, 1; Northampton, 1; total, 3.

Meningitis, pneumococcal, was reported from: Beverly, 1; total, 1.

Meningitis, other forms, was reported from: Boston, 1; total, 1.

Meningitis, undetermined, was reported from: Haverhill, 1; Pittsfield, 1; Sterling, 1; Watertown, 1; total, 4.

Poliomyelitis was reported from: Fall River, 1; Lowell, 1; New Bedford, 1; Saugus, 2; total, 5.

Salmonellosis was reported from: Arlington, 1; Belmont, 4; Boston, 2; Gardner, 1; Salem, 1; Uxbridge, 1; Weymouth, 1; Worcester, 2; total, 13.

Septic sore throat was reported from: Amesbury, 1; Belmont, 1; Boston, 6; Greenfield, 1; Haverhill, 1; Lynn, 1; Medford, 2; Merrimac, 2; Quincy, 1; Reading, 1; Salem, 1; total, 18.

Trichinosis was reported from: Cambridge, 2; Dighton, 1; total, 3.

Typhoid fever was reported from: Beverly, 1; Boston, 1; North Adams, 1; total, 3.

Undulant fever was reported from: Boxford, 1; Dudley, 1; Worcester, 1; total, 3.

BOOK REVIEWS

Howell's Textbook of Physiology. Edited by John F. Fulton, M.D., Sterling Professor of Physiology, Yale University School of Medicine. Fifteenth edition. 8°, cloth, 1304 pp., with 507 illustrations. London: W. B. Saunders Company, 1946. $8.00.

It is a point of much importance that the distinguished Sterling Professor of Physiology at Yale University School of Medicine has undertaken to edit the fifteenth edition of this work, which has been a pacemaker of the subject in this country since its first appearance in 1905. This book, in which functional mechanisms are constantly brought into sharp focus, will be welcomed alike by students and physicians.

The ten sections of the volume include contributions by eminent authorities in their respected fields. Initially, the reader is presented with a brief, concise and thoroughly interesting chapter "Historical Backgrounds of American Physiology" by Dr. Fulton. The titles and the authors of the other sections are as follows: "Principles of Nervous and Muscular Activity," by David P. C. Lloyd; "The Central Nervous System: Motor functions," by John F. Fulton; "The Nervous System: Sensory functions," by Theodore Ruch; "Properties and Constituents of the Blood," by David I. Hitchcock; "Physiology of the Organs of Circulation of the Blood and Lymph," by Donald H. Barron, Harold Lamport and John F. Fulton; "Respiration," by Leslie F. Nims; "Body Fluids and Kidney," by Robert W. Clarke; "Physiology of Digestion and Secretion of the Alimentary Tract," by George R. Cowgill; "Metabolism and Nutrition," by John R. Brobeck; and "Physiology of Reproduction," by William U. Gardner.

This book contains fifty-six chapters. At the end of each chapter there are a number of excellent references. The editor and his collaborators have presented their material in a clear style, offering the complexity of detail and the fluidity of ideas that characterize present-day physiology in a manner that leaves little room for criticism of the authors for the omission of this or that particular subject matter. This book is a refreshing product at the hands of critical scholars and is sure to be of real service to all who study it.

The Bacterial Cell: In its relation to problems of virulence, immunity and chemotherapy. By René J. Dubos. With an addendum by C. F. Robinow. 8°, cloth, 460 pp., illustrated. Cambridge, Massachusetts: Harvard University Press, 1945. $5.00.

This book, a Harvard University Monograph in Medicine and Public Health, is a thoroughly documented expansion of a series of eight lectures delivered in 1944 at the invitation of the Lowell Institute in Boston. The Institute, managed by a single trustee, has long deserved an enviable reputation for its wise and happy choice of lecturers. In selecting Dr. Dubos, at that time George Fabyan Professor of Comparative Pathology and professor of tropical medicine, Schools of Medicine and Public Health, Harvard University, and also a member of the Rockefeller Institute, the high requirements have been fully met — thorough familiarity with the field of knowledge, demonstrated ability in original basic research, and a capacity for lucid exposition. An illustration of the author's philosophic temper is his choice of the quotations that head chapters and sections. In source, these "texts" range from St. Paul's "Epistle to the Corinthians" to Lewis Carroll, and include aphoristic selections from Bacon, Bernard, Cohn, Ehrlich, von Liebig, Pasteur, Renan, Rousseau and Shelley.

The first chapters deal with the complexity of bacterial cells as revealed by direct cytologic examination and reaction to stains. Capsules, flagella, granules, nuclear structures, spores, cell division and colonial characteristics are discussed, with particular attention to their relation to pathogenicity. Revelations provided by electron micrographs are elaborated in the addendum by C. F. Robinow, of Cambridge, England.

Enzymic reactions contribute something to knowledge of bacterial structures. The nature, number and sometimes the architectural location of bacterial antigens have been profitably studied via the action of bacteriophages and the application of serological analysis, especially in connection with pneumococci and Salmonella.

Bacterial variations are considered, on admittedly inadequate evidence, to be probably ascribable to some selective process operating on forms originally present in the parental culture. Concerning the transformation of pneumococcal types, however, it appears that a real genetic mutation is induced by a highly polymerized desoxyribonucleic acid. If the strong evidence upholding this concept turns out to be valid, its discoverers (Avery, MacLeod and McCarty) have made a fundamental contribution that is likely to have wide and profound scientific applications.

The illuminating discussion of virulence and its intricate nature, in terms of modern concepts, is not equaled in any publication that the reviewer has seen. The importance of the host is considered, but Dubos's analysis of infection deals more with antigenic structure, toxins, variations and adaptations. Recognition that virulence is a complex quality and that modification or loss of only one of its components (each readily capable of independent variation) may abolish pathogenicity has the effect of multiplying the points of vulnerability of harmful micro-organisms; this in turn affords a correspondingly increased number of mechanisms with which antibiotic agents may effectively interfere. In the discussion of immunization against infections and in nearly sixty pages given over to bacteriostatic and bactericidal agents this conception is expanded in relation to the multiplicity of immunochemical structures and specificities of cellular components, as well as the intimate nature of such metabolic processes as nutrition, respiration, growth and division.

Most studies of antibiosis have emphasized the effect of various agents on catabolic reactions, but there are a few cases in which it seems that the essential primary effect of the inhibition is on a synthetic anabolic process vitally necessary to bacterial activities. Wider and more detailed studies of bacterial physiology and nutrition are highly desirable, that chemotherapy may advance more logically and rapidly. The mechanisms of drug-fastness receive detailed consideration. The final chapter on trends and perspectives deals chiefly with the nature of specificity and the significance of bacterial variability.

The bibliography comprises about a thousand titles; the text page on which the citation is discussed is also indicated — an especially helpful feature that should be widely copied. Type and presswork are excellent.

Lest all these comments be deemed too uniformly fulsome, the reviewer protests against the use of "haptene." This spelling is probably a mere upshoot from the author's Gallic origin, but it is a retrogressive step toward "toxine," "agglutinine" and so forth, current within the reviewer's memory, and it is an unwarranted meddling with Landsteiner's neologism "hapten."

This is an important book — critical, penetrating, informative, stimulating and, especially, heuristic. Despite the existing primitive and fragmentary knowledge or complete

ignorance of many essential factors, the author has succeeded remarkably in integrating and interpreting information drawn from many fields and pertinent to the biochemical architecture of micro-organisms.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Renal Hypertension. By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Mumoz and Alberto C. Taquini, Institute of Physiology, Faculty of Medical Sciences, and Institute of Cardiology, V. F. Grego Foundation, Buenos Aires, Argentina. Translated by Louis Dexter, M.D. Harvard Medical School and Peter Bent Brigham Hospital. 8°, cloth, 451 pp., with 90 illustrations. Springfield, Illinois: Charles C Thomas, 1946. $6.75.

Ambulatory Proctology. By Alfred J. Cantor, M.D., associate proctologist, Kew Gardens General Hospital, Long Island, New York. With a foreword by Beaumont S. Cornell, M.D., editor, *American Journal of Digestive Diseases.* 8°, cloth, 524 pp., with 281 illustrations. New York and London: Paul B. Hoeber, Incorporated, 1946. $8.00.

Handbook of Neurological Examination and Case Recording. By D. Denny-Brown, M.D., James Jackson Putnam Professor of Neurology, Harvard Medical School. 12°, paper, 112 pp. Cambridge, Massachusetts: Harvard University Press, 1946. $1.75.

Penicillin: Its practical application. Under the general editorship of Sir Alexander Fleming, M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., professor of bacteriology in the University of London, St. Mary's Hospital, London. 8°, cloth, 380 pp., with 59 illustrations. Philadelphia: Blakiston Company, 1946. $7.00.

Introduction to Surgery. By Virginia Kneeland Frantz, M.D., assistant professor of surgery, Columbia University College of Physicians and Surgeons, associate attending surgical pathologist, Presbyterian Hospital, New York City; and Harold Dortic Harvey, M.D., assistant professor of clinical surgery, Columbia University College of Physicians and Surgeons, assistant attending surgeon, Presbyterian Hospital, New York City. 12°, cloth, 216 pp. New York: Oxford University Press, 1946. $2.50.

Myasthenia Gravis. By Dr. Adalberto R. Goni, member of the staff of the Hospital Alvear, Buenos Aires, chief, Medical Clinic of the Sanitary Service of the Post Office, Telephone and Telegraph. Translated by Georgianna Simmons Gittinger. 8°, cloth, 112 pp., with 10 illustrations. Baltimore: Williams and Wilkins Company, 1946. No charge.

Lippincott's Quick Reference Book for Medicine and Surgery: A clinical, diagnostic and therapeutic digest of general medicine, surgery and the specialties, compiled systematically from modern literature. By George E. Rehberger, M.D. Thirteenth edition. 4°, cloth, 1461 pp., with 302 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $15.00.

Western Reserve University Centennial History of the School of Medicine. By Frederick C. Waite, A.M., Ph.D. 8°, cloth, 588 pp., with 15 illustrations and frontispiece. Cleveland: Western Reserve University Press, 1946. $6.00.

The Journal lacks extra copies of the October 3 and November 14, 1946, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the Journal will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, April 9 — Functional Tests in the Diagnosis of Pancreatic Disease. Dr. Martin Nothmann.

Friday, April 11 — Di-isopropyl Fluorophosphate in its Control of Glaucoma. Dr. Edwin B. Dunphy.

Wednesday, April 16 — Clinicopathological Conference. Drs. Robert Williams and H. E. MacMahon.

Friday, April 18 — Studies in Histochemistry. Dr. Henry Bunting.

Wednesday, April 23 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, April 25 — Temporal Arteritis. Dr. Roy C. Crosby.

Wednesday, April 30 — The Relation of Enzyme Chemistry to Some Recent Advances in Chemotherapy. Dr. Gerhardt Schmidt.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

NEW ENGLAND DIABETES ASSOCIATION

The first meeting of the New England Diabetes Association will be held on Wednesday, April 16, at 7:30 p.m., in the Dowling Amphitheater, Boston City Hospital.

PROGRAM

Diabetes and Hyperthyroidism. Drs. Frank N. Allan and Rosemary Murphy.

The Relation between Insulin Sensitivity and Insulin Resistance. Dr. Francis C. Lowell.

Diabetic Coma at the Boston City Hospital. Dr. W. R. Ohler.

Renal Disease in Diabetes. Dr. Stanley Robbins.

A brief business meeting for the purpose of electing officers and directors and adopting a constitution, will follow.

Physicians, surgeons, nurses, dietitians and other scientific workers interested in the problems of diabetes may apply for membership at the meeting or may write for application blanks to the temporary secretary, Dr. James H. Townsend, 330 Mt. Auburn Street, Cambridge.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 10

FRIDAY, APRIL 11

*9:00–10.00 a.m. Di-isopropyl Fluorophosphate in Its Control of Glaucoma. Dr. Edwin B. Dunphy. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H Pratt Diagnostic Hospital.

MONDAY, APRIL 14

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, APRIL 15

12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

(*Notices continued on page xvii*)